```
     FILE 'BIOSIS' ENTERED AT 11:40:04 ON 09 NOV 2006
                ACT ISS729BI1AU/A
                ---------
L1   (       222)SEA ABB=ON  PLU=ON  ROLDAN E?/AU
L2   (        14)SEA ABB=ON  PLU=ON  PEREZ-LLORET A?/AU
L3   (       307)SEA ABB=ON  PLU=ON  VAZQUEZ G?/AU
L4   (       211)SEA ABB=ON  PLU=ON  BOLAND R?/AU
L5   (       266)SEA ABB=ON  PLU=ON  PAPAPOULOS S?/AU
L6             1 SEA ABB=ON  PLU=ON  L1 AND L2 AND L3 AND L4 AND L5
                ---------

     FILE 'DRUGU' ENTERED AT 11:40:21 ON 09 NOV 2006
                ACT ISS729DU1AU/A
                ---------
L7   (        14)SEA ABB=ON  PLU=ON  ROLDAN E?/AU
L8   (         2)SEA ABB=ON  PLU=ON  PEREZ-LLORET A?/AU
L9   (        22)SEA ABB=ON  PLU=ON  VAZQUEZ G?/AU
L10  (        22)SEA ABB=ON  PLU=ON  BOLAND R?/AU
L11  (        42)SEA ABB=ON  PLU=ON  PAPAPOULOS S?/AU
L12            0 SEA ABB=ON  PLU=ON  L7 AND L8 AND L9 AND L10 AND L11
                ---------

     FILE 'HCAPLUS' ENTERED AT 11:40:30 ON 09 NOV 2006
                ACT ISS729HC1AU/A
                ---------
L13             STR
L14  (         3)SEA FAM FUL L13
L15  (        23)SEA ABB=ON  PLU=ON  L14
L16  (       208)SEA ABB=ON  PLU=ON  ROLDAN E?/AU
L17  (        13)SEA ABB=ON  PLU=ON  PEREZ-LLORET A?/AU
L18  (       380)SEA ABB=ON  PLU=ON  VAZQUEZ G?/AU
L19  (       194)SEA ABB=ON  PLU=ON  BOLAND R?/AU
L20  (       130)SEA ABB=ON  PLU=ON  PAPAPOULOS S?/AU
L21           10 SEA ABB=ON  PLU=ON  ((L16 OR L17 OR L18 OR L19 OR L20)) AND
                L15
                ---------

     FILE 'MEDLINE' ENTERED AT 11:40:49 ON 09 NOV 2006
                ACT ISS729MD1AU/A
                ---------
L22  (       201)SEA ABB=ON  PLU=ON  ROLDAN E?/AU
L23  (        19)SEA ABB=ON  PLU=ON  PEREZ-LLORET A?/AU
L24  (       367)SEA ABB=ON  PLU=ON  VAZQUEZ G?/AU
L25  (       196)SEA ABB=ON  PLU=ON  BOLAND R?/AU
L26  (       199)SEA ABB=ON  PLU=ON  PAPAPOULOS S?/AU
L27            0 SEA ABB=ON  PLU=ON  L22 AND L23 AND L24 AND L25 AND L26
                ---------

     FILE 'PHAR' ENTERED AT 11:41:01 ON 09 NOV 2006
                ACT ISS729PH1AU/A
                ---------
L28  (         0)SEA ABB=ON  PLU=ON  ROLDAN E?/AU
L29  (         0)SEA ABB=ON  PLU=ON  PEREZ-LLORET A?/AU
L30  (         0)SEA ABB=ON  PLU=ON  VAZQUEZ G?/AU
L31  (         0)SEA ABB=ON  PLU=ON  BOLAND R?/AU
L32  (         0)SEA ABB=ON  PLU=ON  PAPAPOULOS S?/AU
L33            0 SEA ABB=ON  PLU=ON  (L28 OR L29 OR L30 OR L31 OR L32)
                ---------

     FILE 'USPATFULL' ENTERED AT 11:41:18 ON 09 NOV 2006
```

```
                ACT ISS729UPF1AU/A
              ---------
L34 (          7)SEA ABB=ON  PLU=ON  ROLDAN E?/AU
L35 (          4)SEA ABB=ON  PLU=ON  PEREZ-LLORET A?/AU
L36 (         17)SEA ABB=ON  PLU=ON  VAZQUEZ G?/AU
L37 (         31)SEA ABB=ON  PLU=ON  BOLAND R?/AU
L38            2 SEA ABB=ON  PLU=ON  L34 AND L35 AND L36 AND L37
               ---------

     FILE 'BIOSIS, USPATFULL, HCAPLUS' ENTERED AT 11:43:34 ON 09 NOV 2006
L*** DEL      12 DUP REM L27 L6 L12 L38 L21 L33 (1 DUPLICATE REMOVED)
                    ANSWER '1' FROM FILE BIOSIS
                    ANSWER '2' FROM FILE USPATFULL
                    ANSWERS '3-12' FROM FILE HCAPLUS

     FILE 'BIOSIS' ENTERED AT 11:44:29 ON 09 NOV 2006
                D QUE L6

     FILE 'DRUGU' ENTERED AT 11:44:37 ON 09 NOV 2006
                D QUE L12

     FILE 'HCAPLUS' ENTERED AT 11:44:46 ON 09 NOV 2006
                D QUE L21

     FILE 'MEDLINE' ENTERED AT 11:44:55 ON 09 NOV 2006
                D QUE L27

     FILE 'PHAR' ENTERED AT 11:45:53 ON 09 NOV 2006
                D QUE L33

     FILE 'USPATFULL' ENTERED AT 11:46:07 ON 09 NOV 2006
                D QUE L38

     FILE 'BIOSIS, USPATFULL, HCAPLUS' ENTERED AT 11:46:36 ON 09 NOV 2006
L39            12 DUP REM L27 L6 L12 L38 L21 L33 (1 DUPLICATE REMOVED)
                      ANSWER '1' FROM FILE BIOSIS
                      ANSWER '2' FROM FILE USPATFULL
                      ANSWERS '3-12' FROM FILE HCAPLUS
                D IALL 1
                D IBIB ABS HITSTR 2
                D IBIB ED ABS HITSTR 3-12

     FILE 'BIOSIS' ENTERED AT 11:48:05 ON 09 NOV 2006
                ACT ISS729BI1A/A
               ---------
L40             STR
L41 (          3)SEA FAM FUL L40
L42 (          2)SEA ABB=ON  PLU=ON  L41
L43 (          2)SEA ABB=ON  PLU=ON  LIDADRONIC ACID OR IG 9402
L44            2 SEA ABB=ON  PLU=ON  L42 OR L43
               ---------

     FILE 'DRUGU' ENTERED AT 11:49:43 ON 09 NOV 2006
                ACT ISS729DU1A/A
              ---------
L45             STR
L46 (          3)SEA FAM FUL L45
L47 (          1)SEA ABB=ON  PLU=ON  L46
L48 (          3)SEA ABB=ON  PLU=ON  LIDADRONIC ACID OR IG 9402
L49            3 SEA ABB=ON  PLU=ON  L47 OR L48
```

```
                ---------

     FILE 'HCAPLUS' ENTERED AT 11:49:56 ON 09 NOV 2006
                ACT ISS729HC1A/A
                ---------
L50               STR
L51 (          3)SEA FAM FUL L50
L52 (         23)SEA ABB=ON  PLU=ON  L51
L53 (          5)SEA ABB=ON  PLU=ON  LIDADRONIC ACID/OBI OR IG 9402/OBI OR
                  IG9402/OBI
L54           23 SEA ABB=ON  PLU=ON  (L52 OR L53)
                ---------

     FILE 'MEDLINE' ENTERED AT 11:50:09 ON 09 NOV 2006
                ACT ISS729MD1A/A
                ---------
L55            1 SEA ABB=ON  PLU=ON  LIDADRONIC ACID OR IG 9402
                ---------

     FILE 'PHAR' ENTERED AT 11:50:24 ON 09 NOV 2006
                ACT ISS729PH1A/A
                ---------
L56               STR
L57 (          3)SEA FAM FUL L56
L58 (          1)SEA ABB=ON  PLU=ON  L57
L59 (          1)SEA ABB=ON  PLU=ON  LIDADRONIC ACID OR IG 9402
L60            1 SEA ABB=ON  PLU=ON  (L58 OR L59)
                ---------

     FILE 'USPATFULL' ENTERED AT 11:50:34 ON 09 NOV 2006
                ACT ISS729UPF1A/A
                ---------
L61               STR
L62 (          3)SEA FAM FUL L61
L63 (         14)SEA ABB=ON  PLU=ON  L62
L64 (          7)SEA ABB=ON  PLU=ON  LIDADRONIC ACID OR IG 9402
L65           14 SEA ABB=ON  PLU=ON  (L63 OR L64)
                ---------

     FILE 'BIOSIS' ENTERED AT 11:54:04 ON 09 NOV 2006
                D QUE L44
L66            2 SEA ABB=ON  PLU=ON  L44 NOT L6

     FILE 'DRUGU' ENTERED AT 11:55:50 ON 09 NOV 2006
                D QUE L49
                D QUE NOS
                D QUE L49
L67            3 SEA ABB=ON  PLU=ON  L49 NOT L12

     FILE 'HCAPLUS' ENTERED AT 11:57:23 ON 09 NOV 2006
                D QUE L54
L68           13 SEA ABB=ON  PLU=ON  L54 NOT L21

     FILE 'MEDLINE' ENTERED AT 12:00:34 ON 09 NOV 2006
                D QUE L55 NOS
L69            1 SEA ABB=ON  PLU=ON  L55 NOT L27

     FILE 'PHAR' ENTERED AT 12:01:15 ON 09 NOV 2006
                D QUE L60 NOS
L70            1 SEA ABB=ON  PLU=ON  L60 NOT L33
```

```
     FILE 'USPATFULL' ENTERED AT 12:01:46 ON 09 NOV 2006
                D QUE L65 NOS
L71            12 SEA ABB=ON  PLU=ON  L65 NOT L38

     FILE 'MEDLINE, BIOSIS, DRUGU, USPATFULL, HCAPLUS, PHAR' ENTERED AT
     12:03:22 ON 09 NOV 2006
L72            30 DUP REM L69 L66 L67 L71 L68 L70 (2 DUPLICATES REMOVED)
                    ANSWER '1' FROM FILE MEDLINE
                    ANSWER '2' FROM FILE BIOSIS
                    ANSWERS '3-5' FROM FILE DRUGU
                    ANSWERS '6-17' FROM FILE USPATFULL
                    ANSWERS '18-29' FROM FILE HCAPLUS
                    ANSWER '30' FROM FILE PHAR


=>
```

=> FILE REG
FILE 'REGISTRY' ENTERED AT 10:23:27 ON 09 NOV 2006
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 8 NOV 2006 HIGHEST RN 912757-80-3
DICTIONARY FILE UPDATES: 8 NOV 2006 HIGHEST RN 912757-80-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

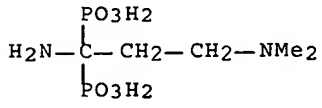
Please note that search-term pricing does apply when
conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> D IDE

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN 63132-38-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN **Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI)**
(CA INDEX NAME)
OTHER NAMES:
CN IG 9402
CN Lidadronic acid
MF C5 H16 N2 O6 P2
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, DDFU, DRUGU,
IFICDB, IFIPAT, IFIUDB, PHAR, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

21 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
21 REFERENCES IN FILE CAPLUS (1907 TO DATE)

```
=> => FILE BIOSIS
FILE 'BIOSIS' ENTERED AT 11:44:29 ON 09 NOV 2006
Copyright (c) 2006 The Thomson Corporation

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 8 November 2006 (20061108/ED)


=> D QUE L6
L1   (       222)SEA FILE=BIOSIS ABB=ON  PLU=ON  ROLDAN E?/AU
L2   (        14)SEA FILE=BIOSIS ABB=ON  PLU=ON  PEREZ-LLORET A?/AU
L3   (       307)SEA FILE=BIOSIS ABB=ON  PLU=ON  VAZQUEZ G?/AU
L4   (       211)SEA FILE=BIOSIS ABB=ON  PLU=ON  BOLAND R?/AU
L5   (       266)SEA FILE=BIOSIS ABB=ON  PLU=ON  PAPAPOULOS S?/AU
L6             1 SEA FILE=BIOSIS ABB=ON  PLU=ON  L1 AND L2 AND L3 AND L4 AND L5



=> FILE DRUGU
FILE 'DRUGU' ENTERED AT 11:44:37 ON 09 NOV 2006
COPYRIGHT (C) 2006 THE THOMSON CORPORATION

FILE LAST UPDATED: 6 NOV 2006        <20061106/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<


=> D QUE L12
L7   (        14)SEA FILE=DRUGU ABB=ON  PLU=ON  ROLDAN E?/AU
L8   (         2)SEA FILE=DRUGU ABB=ON  PLU=ON  PEREZ-LLORET A?/AU
L9   (        22)SEA FILE=DRUGU ABB=ON  PLU=ON  VAZQUEZ G?/AU
L10  (        22)SEA FILE=DRUGU ABB=ON  PLU=ON  BOLAND R?/AU
L11  (        42)SEA FILE=DRUGU ABB=ON  PLU=ON  PAPAPOULOS S?/AU
L12            0 SEA FILE=DRUGU ABB=ON  PLU=ON  L7 AND L8 AND L9 AND L10 AND
                   L11


=> FILE HCAPLUS
FILE 'HCAPLUS' ENTERED AT 11:44:46 ON 09 NOV 2006
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strictly prohibited.

FILE COVERS 1907 - 9 Nov 2006  VOL 145 ISS 20
```
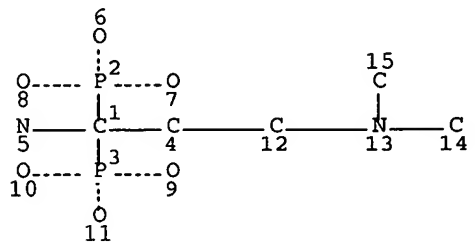

FILE LAST UPDATED: 8 Nov 2006 (20061108/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> D QUE L21
L13 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE
L14 (3)SEA FILE=REGISTRY FAM FUL L13
L15 (23)SEA FILE=HCAPLUS ABB=ON PLU=ON L14
L16 (208)SEA FILE=HCAPLUS ABB=ON PLU=ON ROLDAN E?/AU
L17 (13)SEA FILE=HCAPLUS ABB=ON PLU=ON PEREZ-LLORET A?/AU
L18 (380)SEA FILE=HCAPLUS ABB=ON PLU=ON VAZQUEZ G?/AU
L19 (194)SEA FILE=HCAPLUS ABB=ON PLU=ON BOLAND R?/AU
L20 (130)SEA FILE=HCAPLUS ABB=ON PLU=ON PAPAPOULOS S?/AU
L21 10 SEA FILE=HCAPLUS ABB=ON PLU=ON ((L16 OR L17 OR L18 OR L19 OR L20)) AND L15

=> FILE MEDLINE
FILE 'MEDLINE' ENTERED AT 11:44:55 ON 09 NOV 2006

FILE LAST UPDATED: 8 Nov 2006 (20061108/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> D QUE L27
L22 (       201)SEA FILE=MEDLINE ABB=ON  PLU=ON  ROLDAN E?/AU
L23 (        19)SEA FILE=MEDLINE ABB=ON  PLU=ON  PEREZ-LLORET A?/AU
L24 (       367)SEA FILE=MEDLINE ABB=ON  PLU=ON  VAZQUEZ G?/AU
L25 (       196)SEA FILE=MEDLINE ABB=ON  PLU=ON  BOLAND R?/AU
L26 (       199)SEA FILE=MEDLINE ABB=ON  PLU=ON  PAPAPOULOS S?/AU
L27           0 SEA FILE=MEDLINE ABB=ON  PLU=ON  L22 AND L23 AND L24 AND L25
                AND L26


=> FILE PHAR
FILE 'PHAR' ENTERED AT 11:45:53 ON 09 NOV 2006
COPYRIGHT (C) 2006 Informa UK Ltd.

FILE RELOADED May 4, 2003
FILE LAST UPDATED:  Nov 6, 2006 (20061106/ED)
```

A new therapeutic code has been added to PHAR. See HELP THRCODES for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

SUBSCRIBER DISCOUNT AVAILABLE

Informa UK is offering a discount in the PHAR file to customers who currently subscribe to Pharmaprojects at their particular site. If you are a Pharmaprojects subscriber, please send us your STN Account number and we will apply the discount to those sites who qualify.

Please fax your complete name, address, and STN Account number to our Customer Support Group at: 614-447-3751 or email help@cas.org.

```
=> D QUE L33
L28 (         0)SEA FILE=PHAR ABB=ON  PLU=ON  ROLDAN E?/AU
L29 (         0)SEA FILE=PHAR ABB=ON  PLU=ON  PEREZ-LLORET A?/AU
L30 (         0)SEA FILE=PHAR ABB=ON  PLU=ON  VAZQUEZ G?/AU
L31 (         0)SEA FILE=PHAR ABB=ON  PLU=ON  BOLAND R?/AU
L32 (         0)SEA FILE=PHAR ABB=ON  PLU=ON  PAPAPOULOS S?/AU
L33           0 SEA FILE=PHAR ABB=ON  PLU=ON  (L28 OR L29 OR L30 OR L31 OR
                L32)


=> FILE USPATFULL
FILE 'USPATFULL' ENTERED AT 11:46:07 ON 09 NOV 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 9 Nov 2006 (20061109/PD)
FILE LAST UPDATED: 9 Nov 2006 (20061109/ED)
HIGHEST GRANTED PATENT NUMBER: US7134145
HIGHEST APPLICATION PUBLICATION NUMBER: US2006253949
CA INDEXING IS CURRENT THROUGH 7 Nov 2006 (20061107/UPCA)
```

ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 9 Nov 2006 (20061109/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006

=> D QUE L38
L34 (7)SEA FILE=USPATFULL ABB=ON PLU=ON ROLDAN E?/AU
L35 (4)SEA FILE=USPATFULL ABB=ON PLU=ON PEREZ-LLORET A?/AU
L36 (17)SEA FILE=USPATFULL ABB=ON PLU=ON VAZQUEZ G?/AU
L37 (31)SEA FILE=USPATFULL ABB=ON PLU=ON BOLAND R?/AU
L38 2 SEA FILE=USPATFULL ABB=ON PLU=ON L34 AND L35 AND L36 AND L37

=> DUP REM L27 L6 L12 L38 L21 L33
L27 HAS NO ANSWERS
L12 HAS NO ANSWERS
L33 HAS NO ANSWERS
DUPLICATE IS NOT AVAILABLE IN 'PHAR'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
FILE 'BIOSIS' ENTERED AT 11:46:36 ON 09 NOV 2006
Copyright (c) 2006 The Thomson Corporation

FILE 'USPATFULL' ENTERED AT 11:46:36 ON 09 NOV 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'HCAPLUS' ENTERED AT 11:46:36 ON 09 NOV 2006
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COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L27
PROCESSING COMPLETED FOR L6
PROCESSING COMPLETED FOR L12
PROCESSING COMPLETED FOR L38
PROCESSING COMPLETED FOR L21
PROCESSING COMPLETED FOR L33
L39 12 DUP REM L27 L6 L12 L38 L21 L33 (1 DUPLICATE REMOVED)
ANSWER '1' FROM FILE BIOSIS
ANSWER '2' FROM FILE USPATFULL
ANSWERS '3-12' FROM FILE HCAPLUS

=> D IALL 1; D IBIB ABS HITSTR 2; D IBIB ED ABS HITSTR 3-12

L39 ANSWER 1 OF 12 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
DUPLICATE 1
ACCESSION NUMBER: 2003:434007 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300434007
TITLE: Uses of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid.
AUTHOR(S): **Roldan, Emilio J. A.** [Inventor, Reprint Author]; **Perez-Lloret, Anibal** [Inventor]; **Vazquez, Guillermo** [Inventor]; **Boland, Ricardo** [Inventor]; **Papapoulos, Sokrates E.** [Inventor]
CORPORATE SOURCE: Buenos Aires, Argentina
ASSIGNEE: Gador, S.A., Argentina; University of Leiden, Netherlands
PATENT INFORMATION: US 6605603 20030812
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Aug 12 2003) Vol. 1273, No. 2. http://www.uspto.gov/web/menu/patdata.html. e-file.

ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Sep 2003
Last Updated on STN: 17 Sep 2003
ABSTRACT:The present invention relates to novel uses of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid or any of its soluble salts or any of its hydrates, in particular its use for the manufacture of a medicament for selective modulation of osteoblasts.
NAT. PATENT. CLASSIF.:514103000
CONCEPT CODE: Pathology - Therapy 12512
Pharmacology - General 22002
INDEX TERMS: Major Concepts
Methods and Techniques; Pharmaceuticals (Pharmacology)
INDEX TERMS: Chemicals & Biochemicals
1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid: intermediate, osteoblast modulation medicament, pharmaceutical
INDEX TERMS: Methods & Equipment
osteoblast modulation medicament manufacture: applied and field techniques

L39 ANSWER 2 OF 12 USPATFULL on STN
ACCESSION NUMBER: 2004:31789 USPATFULL Full-text
TITLE: Uses of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid
INVENTOR(S): **Roldan, Emilio J.A.**, Buenos Aires, ARGENTINA
Perez-Lloret, Anibal, Buenos Aires, ARGENTINA
Vazquez, Guillermo, San Juan, ARGENTINA
Boland, Ricardo, San Juan, ARGENTINA
Papapoulos, Sokrates E., Leiden, NETHERLANDS

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004023931	A1	20040205
APPLICATION INFO.:	US 2003-619729	A1	20030715 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2001-830734, filed on 27 Jul 2001, GRANTED, Pat. No. US 6605603 A 371 of International Ser. No. WO 1998-EP9908269, filed on 30 Oct 1998, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	AR 1998-980105446	19981030

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PENDORF & CUTLIFF, 5111 Memorial Highway, Tampa, FL, 33634-7356
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 923
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a method for maintaining a healthy bone structure by administering to a patient a bone health promoting effective amount of a medicament containing 1-amino-3-(N,N- dimethylamino)-

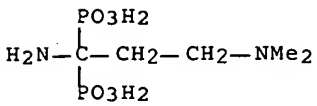
propylidene-1,1-bisphosphonic acid, any of its soluble salts or any of its hydrates.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L39 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:207839 HCAPLUS Full-text
DOCUMENT NUMBER: 142:274072
TITLE: Use of bisphosphonates for the treatment of osteogenesis imperfecta
INVENTOR(S): **Roldan, Emilio J. A.; Perez, Lloret Anibal**
PATENT ASSIGNEE(S): Gador, S.A., Argent.
SOURCE: U.S., 14 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

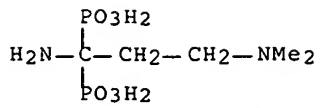
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6864228	B1	20050308	US 2000-570275	20000512
US 2005026870	A1	20050203	US 2004-931858	20040901
PRIORITY APPLN. INFO.:			AR 1999-102331 A	19990512
			US 2000-570275 A3	20000512

ED Entered STN: 09 Mar 2005
AB This procedure consists in the first stage, of the administration of enough quantity of bisphosphonate preparation during the necessary period of time to acquire a degree of volumetric mineral d. of the cortical tissue of application, within the normal range (average IDS). Then the administration of the bisphosphonate preparation is interruption in order to enable the development of the sectional momentum of inertia. The length of the second stage can be determined by means of a tomog. That is to say, that the periods of administration or non-administration of the mineralizing agent are defined or controlled by precise osteol. variables and therefore are not fixed. If during the second stage the cortical mineral d. drops by 6-10% of the maximum value previously obtained, administration of bisphosphonate preparation should be resumed until the corresponding maximum adjusted value is reached again. The proposed procedure of a period with bisphosphonate followed by another period without the bisphosphonate agent improves fracture resistance, provided that the length of both periods is controlled by defined osteol. variables.
IT **63132-38-7**, IG 9402
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bisphosphonates sequential administration for treatment of osteogenesis imperfecta)
RN 63132-38-7 HCAPLUS
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:214345 HCAPLUS Full-text
DOCUMENT NUMBER: 139:143853
TITLE: Modulation of Cytosolic Calcium Levels in Osteoblast-like Osteosarcoma Cells by Olpadronate and its Amino-Derivative IG-9402
AUTHOR(S): **Vazquez, G.**; Santillan, G.; **Boland, R.**; **Roldan, E.**; **Perez-Lloret, A.**
CORPORATE SOURCE: Departamento de Biologia, Bioquimica y Farmacia, Universidad Nacional del Sur, Bahia Blanca, 8000, Argent.
SOURCE: Calcified Tissue International (2003), 72(3), 215-221
CODEN: CTINDZ; ISSN: 0171-967X
PUBLISHER: Springer-Verlag New York Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 19 Mar 2003
AB The mol. mechanisms as well as the structure/activity relationships involved in the antiresorptive actions of bisphosphonates on bone cells are still not clear. Replacement of the R1-hydroxyl by an NH2 group in olpadronate (OPD) abolishes its antiresorptive activity. We show here that in the rat osteosarcoma-derived osteoblast-like ROS 17/2.8 cell line, OPD and IG-9402 (NH2-OPD; [3-(N,N-dimethylamine)-1-aminopropylidene bisphosphonate]), similar to 1,25(OH)2-vitamin D3, rapidly modulate cytosolic calcium levels ([Ca2+]i). As for the steroid hormone, the osteosarcoma cell Ca2+i response to OPD was rapid (30 s) and sustained (>5 min), exhibiting a biphasic profile. The response to IG-9402 was also fast but smaller than that of OPD and 1,25(OH)2D3, and rapidly declined to levels near basal. The effect of these bisphosphonates on [Ca2+]i was dose-dependent, being maximal at 108 M and was not observed in non-bone cellular systems, e.g., skeletal muscle and breast cells. Pretreatment of the ROS 17/2.8 cells with the Ca2+ channel blockers nifedipine and verapamil markedly reduced (>70%) the influx phase of the response to OPD and almost completely inhibited that of IG-9402, indicating the participation of voltage-dependent Ca2+ channels in the action of both compds. Moreover, preincubation with the phospholipase C inhibitors U73122 and neomycin or depletion of inner stores with thapsigargin completely blocked the response to either olpadronate or its amino-derivative Both OPD and IG-9402 significantly increased osteocalcin release into the culture medium of osteosarcoma cells. The results support the involvement of the Ca2+ signaling pathway as part of the mechanism by which bisphosphonates induce bone cellular responses.
IT **63132-38-7**, IG 9402
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modulation of cytosolic calcium levels in osteoblast-like osteosarcoma cells by olpadronate and its amino-derivative IG-9402)
RN 63132-38-7 HCAPLUS
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:574937 HCAPLUS Full-text
DOCUMENT NUMBER: 137:129902
TITLE: Composition comprising bisphosphonates for prevention and/or treatment of metabolic diseases of bones
INVENTOR(S): Zanetti, Daniel; Cairatti, Damian; Piccinni, Enrique; **Roldan, Emilio J. A.; Papapoulos, Socrates**
PATENT ASSIGNEE(S): Gador S.A., Argent.; University of Leiden
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

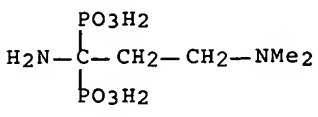
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002058708	A1	20020801	WO 2001-EP690	20010123
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2431515	AA	20020801	CA 2001-2431515	20010123
EP 1372669	A1	20040102	EP 2001-911512	20010123
EP 1372669	B1	20050615		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001016865	A	20040225	BR 2001-16865	20010123
JP 2004519463	T2	20040702	JP 2002-559042	20010123
AT 297740	E	20050715	AT 2001-911512	20010123
ES 2243457	T3	20051201	ES 2001-1911512	20010123
US 2004087550	A1	20040506	US 2003-466897	20031212
PRIORITY APPLN. INFO.:			WO 2001-EP690 W	20010123

ED Entered STN: 02 Aug 2002
AB The present invention relates to a composition for prevention and/or treatment of metabolic diseases of bones comprising at least one bisphosphonate; viscosity agents comprising CM-cellulose and xanthan gum; at least one flavoring agent; and purified water; a process for preparing a composition according to the present invention; and use of such a composition for prevention, treatment and/or diagnosis of metabolic diseases of bones, especially for children. A composition contained sodium alendronate, Avicel RC591, xanthan gum and other excipients to form a solution
IT **63132-38-7**

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(composition comprising bisphosphonates for prevention and/or treatment of metabolic diseases of bones)

RN 63132-38-7 HCAPLUS

CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:41395 HCAPLUS Full-text

DOCUMENT NUMBER: 137:210865

TITLE: Bisphosphonates suppress bone resorption by a direct effect on early osteoclast precursors without affecting the osteoclastogenic capacity of osteogenic cells: the role of protein geranylgeranylation in the action of nitrogen-containing bisphosphonates on osteoclast precursors

AUTHOR(S): Van Beek, E. R.; Lowik, C. W. G. M.; **Papapoulos, S. E.**

CORPORATE SOURCE: Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, Neth.

SOURCE: Bone (New York, NY, United States) (2002), 30(1), 64-70
CODEN: BONEDL; ISSN: 8756-3282

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 16 Jan 2002

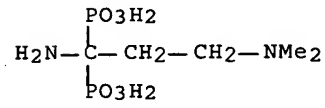
AB Nitrogen-containing bisphosphonates (NBps) are taken up by osteoclasts and inhibit farnesyl pyrophosphate synthase, an enzyme of the mevalonate pathway. There is evidence, however, that cells other than mature osteoclasts, like osteoclast precursors and osteoblasts, are also involved in the action of Bps on bone resorption in vitro. To examine this issue further, we developed a new in vitro model, which allows the study of the effects of additives on early osteoclast precursors. In this model, osteogenic cells are essential for osteoclastogenesis. The model consists of 15-day-old fetal mouse metatarsals. At time of explantation, these bone rudiments do not yet contain a mineralized matrix or osteoclasts; only early osteoclast precursors are present in the perichondrium. During culture and after the addition of Naβ-glycerolphosphate, the bones form a mineralized matrix that is consequently resorbed by osteoclasts that develop from their precursors. Short treatment of these explants with Bps, before the formation of a mineralized matrix, resulted in a subsequent dose-dependent inhibition of bone resorption. The relative potencies of eight Bps to suppress resorption were comparable with those observed after the addition of Bps after the formation of a mineralized matrix, the natural target of Bps. In addition, the effects of the NBp olpadronate, but not of clodronate, on osteoclastic resorption, could be partly reversed by geranylgeraniol. Results indicate that Bps can suppress

osteoclastic resorption in vitro by a direct action on very early osteoclast precursors at the bone surface, and not by affecting the osteoclastogenic capacity of osteogenic cells. Moreover, the mechanism of action of the NBp olpadronate, but not clodronate, on early tartrate-resistant acid phosphatase-neg. osteoclast precursors involves inhibition of protein geranylgeranylation, indicating a mol. mechanism similar to that established for mature osteoclasts.

IT **63132-38-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bisphosphonates suppress bone resorption by a direct effect on early osteoclast precursors without affecting osteoclastogenic capacity of osteogenic cells)

RN 63132-38-7 HCAPLUS

CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:314554 HCAPLUS Full-text
DOCUMENT NUMBER: 132:318061
TITLE: 1-Amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for medicament for osteoblast modulation
INVENTOR(S): **Roldan, Emilio J. A.; Perez-Lloret, Anibal; Vazquez, Guillermo; Boland, Ricardo; Papapoulos, Sokrates E.**
PATENT ASSIGNEE(S): Gador S.A., Argent.; University of Leiden
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000025794	A1	20000511	WO 1999-EP8269	19991029
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2346171	AA	20000511	CA 1999-2346171	19991029
CA 2346171	C	20060117		

EP 1137419	A1	20011004	EP 1999-955918		19991029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
TR 200101176	T2	20020221	TR 2001-200101176		19991029
JP 2003524606	T2	20030819	JP 2000-579234		19991029
AU 771081	B2	20040311	AU 2000-12675		19991029
ZA 2001003404	A	20020314	ZA 2001-3404		20010426
US 6605603	B1	20030812	US 2001-830734		20010727
BR 2001006921	A	20041103	BR 2001-6921		20011015
US 2004023931	A1	20040205	US 2003-619729		20030715
PRIORITY APPLN. INFO.:			AR 1998-105446	A	19981030
			WO 1999-EP8269	W	19991029
			US 2001-830734	A3	20010727

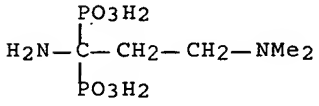
ED Entered STN: 15 May 2000

AB The invention relates to the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid (amino-substituted form of olpadronate), or a soluble salt or hydrate thereof, in particular for the manufacture of a medicament for selective modulation of osteoblasts.

IT **63132-38-7 63132-38-7D**, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for osteoblast modulation)

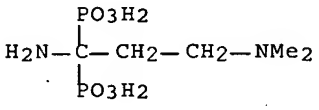
RN 63132-38-7 HCAPLUS

CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



RN 63132-38-7 HCAPLUS

CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:808502 HCAPLUS Full-text

DOCUMENT NUMBER: 133:344627

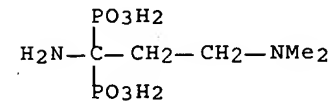
TITLE: Use of bisphosphate for the treatment of osteogenesis imperfecta

INVENTOR(S): **Roldan, Emilio J. A.; Perez-Lloret,**

Anibal
PATENT ASSIGNEE(S): Gador S.A., Argent.
SOURCE: Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

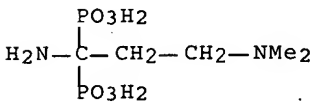
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1051976	A2	20001115	EP 2000-110056	20000512
EP 1051976	A3	20021023		
EP 1051976	B1	20050330		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2308532	AA	20001112	CA 2000-2308532	20000511
CA 2308532	C	20051129		
AT 291921	E	20050415	AT 2000-110056	20000512
ES 2238950	T3	20050916	ES 2000-110056	20000512
PRIORITY APPLN. INFO.:			AR 1999-102331 A	19990512

ED Entered STN: 17 Nov 2000
AB The present invention is related to the use of a bisphosphonate for the manufacture of a medicament for the treatment of osteogenesis imperfecta characterized in that the bisphosphonate is administered in a first stage and the bisphosphonate is not administered in a second stage, wherein the first stage is for obtaining a defined bone mineral d. and the second stage is for architectonic expansion of the bone. An example is given showing specific improvement of conical mineral d. on administration of bisphosphonates.
IT **63132-38-7**, IG 9402
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(IG 9402; bisphosphates for treatment of osteogenesis imperfecta)
RN 63132-38-7 HCAPLUS
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



L39 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:140267 HCAPLUS Full-text
DOCUMENT NUMBER: 130:332835
TITLE: Nitrogen-containing bisphosphonates inhibit isopentenyl pyrophosphate isomerase/farnesyl pyrophosphate synthase activity with relative potencies corresponding to their antiresorptive potencies in vitro and in vivo
AUTHOR(S): Van Beek, Ermond; Pieterman, Elsbet; Cohen, Louis; Lowik, Clemens; **Papapoulos, Socrates**
CORPORATE SOURCE: Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, 2333 AA, Neth.
SOURCE: Biochemical and Biophysical Research Communications

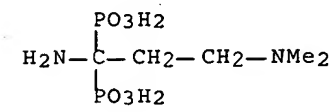
(1999), 255(2), 491-494
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 05 Mar 1999
AB Bisphosphonates, synthetic compds. which suppress bone resorption, are used in the treatment of skeletal disorders. Their mode of action and intracellular targets have not yet been identified. Recent evidence suggested that enzymes of the mevalonate pathway are the potential targets. In this study, we examined the effect of four potent nitrogen (N)-containing bisphosphonates, clodronate and NH2-olpadronate, an inactive analog of olpadronate, on isopentenyl pyrophosphate isomerase/farnesyl pyrophosphate synthase, geranylgeranyl pyrophosphate synthase, and protein geranylgeranyl transferase I activity. We found that all N-containing bisphosphonates inhibited isopentenyl pyrophosphate isomerase/farnesyl pyrophosphate synthase activity dose dependently with relative potencies corresponding to their anti-resorptive potencies in vitro and in vivo, whereas clodronate and NH2-olpadronate had no effect. Furthermore, none of the bisphosphonates tested affected geranylgeranyl pyrophosphate synthase or geranylgeranyl transferase I activity. Our study reveals for the first time the intracellular target of N-containing bisphosphonates and supports the view that all bisphosphonates do not share the same mol. mechanism of action. (c) 1999 Academic Press.
IT **63132-38-7**, NH2-olpadronate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrogen-containing bisphosphonates inhibit IPP isomerase/FPP synthase activity with relative potencies corresponding to their antiresorptive potencies in vitro and in vivo)
RN 63132-38-7 HCAPLUS
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:130639 HCAPLUS Full-text
DOCUMENT NUMBER: 128:228387
TITLE: Differential effects of aminosubstituted analogs of hydroxy bisphosphonates on the growth of Dictyostelium discoideum
AUTHOR(S): Brown, R. J.; Van Beek, E.; Watts, D. J.; Lowik, C. W. G. M.; **Papapoulos, S. E.**
CORPORATE SOURCE: Department of Molecular Biology and Biotechnology, University of Sheffield, Sheffield, UK
SOURCE: Journal of Bone and Mineral Research (1998), 13(2), 253-258
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: Blackwell Science, Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 05 Mar 1998
AB Replacing the hydroxyl group in the bone-binding site of three clin. useful bisphosphonates (etidronate, pamidronate, and olpadronate) by an amino group resulted in great differences in their antiresorptive potencies in vitro. In the present study, this is also shown in vivo in mice treated with the six bisphosphonates at doses of up to 16 μM/kg/day for 12 days. Because binding to bone mineral is nearly the same for all tested bisphosphonates, these findings suggest that the aminosubstitution affects the cellular action of the bisphosphonates. This was tested in the cellular slime mold Dictyostelium discoideum in which cellular effects of bisphosphonates can be examined independently of binding to bone mineral. Etidronate and its aminosubstituted analog were equipotent in inhibiting amebal growth, while pamidronate was somewhat more potent than its analog. Whereas olpadronate was a potent inhibitor of axenic growth of Dictyostelium amebae, the aminosubstitution reduced its potency drastically (IC50 12 μM and 700 μM, resp.). The similarities between the inhibitory effects of the bisphosphonates tested on bone resorption in vitro and in vivo and on the growth of Dictyostelium amebae confirm that the differences in antiresorptive potencies found reflect differences in cellular effects and suggest that bisphosphonates may bind to more than one intracellular target.
IT **63132-38-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(differential effects of amino-substituted analogs of hydroxy bisphosphonates on growth of Dictyostelium discoideum)
RN 63132-38-7 HCAPLUS
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:132766 HCAPLUS Full-text
DOCUMENT NUMBER: 126:144414
TITLE: Amino-substituted bisphosphonic acids
INVENTOR(S): **Papapoulos, Socrates**; Van Beek, E. R.; Lowick, C. W. G. M.; Labriola, Rafael; Vecchioli, Adriana
PATENT ASSIGNEE(S): Gador S.A., Argent.; University of Leiden
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

EP 753523	A1	19970115	EP 1995-110706	19950710
R: GB				
WO 9702827	A1	19970130	WO 1996-EP2981	19960708
W: AU, BR, CA, CN, CZ, FI, IL, JP, KP, KR, NO, PL, RU, SK, US, VN				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9666125	A1	19970210	AU 1996-66125	19960708
EP 837682	A1	19980429	EP 1996-925679	19960708
EP 837682	B1	20021106		
R: DE, FR, GB, NL				
JP 11508905	T2	19990803	JP 1996-505494	19960708
ZA 9605798	A	19980109	ZA 1996-5798	19960709
US 5990098	A	19991123	US 1998-983247	19980901
PRIORITY APPLN. INFO.:			EP 1995-110706 A	19950710
			WO 1996-EP2981 W	19960708

OTHER SOURCE(S): MARPAT 126:144414

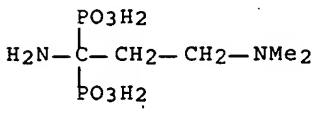
ED Entered STN: 28 Feb 1997

AB 1-Aminoalkylidene-1,1-bisphosphonic acids, RC(NH2)[P(O)(OH)2]2 (R = C1-9 straight-chain or branched aliphatic hydrocarbon radical which is optionally substituted by one or more amino or aminoalkyl groups with the exception of a terminal aminoalkyl group NR1R2; R1 = C1-9 straight-chain or branched, saturated or unsatd. aliphatic hydrocarbon radical, R2 = cyclohexyl or cyclohexylmethyl, benzyl or a straight-chain or branched, C4-18 saturated or unsatd. aliphatic hydrocarbon radical, as a single substituent of R) or any salts thereof, useful for treatment of disorders of calcium and bone metabolism, is described. Thus, hydrolysis of PCl3 gave phosphorus acid which on treatment with MeCN in MeOH followed by acidic workup gave 100% MeC(NH2)[P(O)(OH)2]2. Some binding of compds. prepared with bone materials is described.

IT **63132-38-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and bone binding activity of amino-substituted bisphosphonic acids)

RN 63132-38-7 HCAPLUS

CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



L39 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:642672 HCAPLUS Full-text

DOCUMENT NUMBER: 125:316217

TITLE: Dissociation of binding and antiresorptive properties of hydroxybisphosphonates by substitution of the hydroxyl with an amino group

AUTHOR(S): Van Beek, Ermond; Lowik, Clemens; Que, Ivo; **Papapoulos, Socrates**

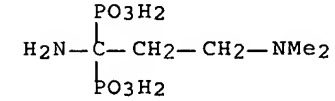
CORPORATE SOURCE: Department Endocrinology and Metabolic Diseases, University Hospital, Leiden, Neth.

SOURCE: Journal of Bone and Mineral Research (1996), 11(10), 1492-1497
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 31 Oct 1996

AB The purpose of this study was to examine the role of the R1 moiety of bisphosphonates in binding to bone mineral and for antiresorptive action. For this, the R1 chain of three clin. useful hydroxybisphosphonates (etidronate, pamidronate, and olpadronate) was substituted with an amino group. The effects of the amino-substituted bisphosphonates were compared with those of their hydroxy counterparts in a crystal growth assay and in fetal mouse long bone cultures which are representative of bisphosphonate actions in vivo. It was found that all three amino-substituted compds. and their hydroxy analogs bound with similar affinity to bone mineral and inhibited the growth of calcium oxalate crystals to the same extent. Surprisingly, the antiresorptive effect of olpadronate was totally abolished by the amino substitution of the hydroxyl group while that of pamidronate was reduced by about six-fold and that of etidronate did not change. These studies demonstrate the involvement of the entire bisphosphonate mol. in the cellular mechanism of antiresorptive action. In addition, the amino-substituted analog of olpadronate, which lacks any antiresorptive action but retains all other properties of olpadronate, provides an excellent tool for the study of specific cellular effects involved in bisphosphonate action.

IT **63132-38-7**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(dissociation of bone mineral binding and antiresorptive properties of hydroxybisphosphonates by substitution of hydroxyl with amino group)

RN 63132-38-7 HCAPLUS
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



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=> => FILE BIOSIS
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 8 November 2006 (20061108/ED)


=> D QUE L44


STEREO ATTRIBUTES: NONE
L41 (         3)SEA FILE=REGISTRY FAM FUL L40
L42 (         2)SEA FILE=BIOSIS ABB=ON  PLU=ON  L41
L43 (         2)SEA FILE=BIOSIS ABB=ON  PLU=ON  LIDADRONIC ACID OR IG 9402
L44           2 SEA FILE=BIOSIS ABB=ON  PLU=ON  L42 OR L43


=> S L44 NOT L6
L66           2 L44 NOT L6

=> FILE DRUGU
FILE 'DRUGU' ENTERED AT 11:55:50 ON 09 NOV 2006
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FILE LAST UPDATED: 6 NOV 2006        <20061106/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<


=> D QUE L49


STEREO ATTRIBUTES: NONE
L46 (         3)SEA FILE=REGISTRY FAM FUL L45
L47 (         1)SEA FILE=DRUGU ABB=ON  PLU=ON  L46
L48 (         3)SEA FILE=DRUGU ABB=ON  PLU=ON  LIDADRONIC ACID OR IG 9402
L49           3 SEA FILE=DRUGU ABB=ON  PLU=ON  L47 OR L48

=> S L49 NOT L12
L67           3 L49 NOT L12

=> FILE HCAPLUS
FILE 'HCAPLUS' ENTERED AT 11:57:23 ON 09 NOV 2006
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FILE COVERS 1907 - 9 Nov 2006 VOL 145 ISS 20
FILE LAST UPDATED: 8 Nov 2006 (20061108/ED)

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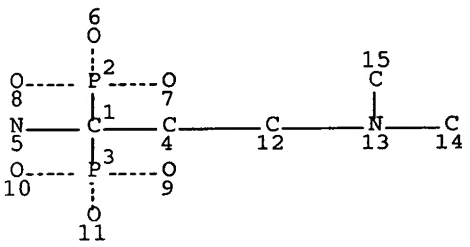
'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> D QUE L54
L50 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE
L51 (3) SEA FILE=REGISTRY FAM FUL L50
L52 (23) SEA FILE=HCAPLUS ABB=ON PLU=ON L51
L53 (5) SEA FILE=HCAPLUS ABB=ON PLU=ON LIDADRONIC ACID/OBI OR IG
9402/OBI OR IG9402/OBI
L54 23 SEA FILE=HCAPLUS ABB=ON PLU=ON (L52 OR L53)

=> S L54 NOT L21
L68 13 L54 NOT L21

=> FILE MEDLINE
FILE 'MEDLINE' ENTERED AT 12:00:34 ON 09 NOV 2006

FILE LAST UPDATED: 8 Nov 2006 (20061108/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details
on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary..

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> D QUE L55 NOS
L55             1 SEA FILE=MEDLINE ABB=ON  PLU=ON  LIDADRONIC ACID OR IG 9402


=> S L55 NOT L27
L69             1 L55 NOT L27

=> FILE PHAR
FILE 'PHAR' ENTERED AT 12:01:15 ON 09 NOV 2006
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FILE RELOADED May 4, 2003
FILE LAST UPDATED:  Nov 6, 2006 (20061106/ED)
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A new therapeutic code has been added to PHAR. See HELP THRCODES for details.

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Please fax your complete name, address, and STN Account number to our Customer Support Group at: 614-447-3751 or email help@cas.org.

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=> D QUE L60 NOS
L56               STR
L57 (           3)SEA FILE=REGISTRY FAM FUL L56
L58 (           1)SEA FILE=PHAR ABB=ON  PLU=ON  L57
L59 (           1)SEA FILE=PHAR ABB=ON  PLU=ON  LIDADRONIC ACID OR IG 9402
L60             1 SEA FILE=PHAR ABB=ON  PLU=ON  (L58 OR L59)


=> S L60 NOT L33
L70             1 L60 NOT L33

=> FILE USPATFULL
FILE 'USPATFULL' ENTERED AT 12:01:46 ON 09 NOV 2006
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 9 Nov 2006 (20061109/PD)
FILE LAST UPDATED: 9 Nov 2006 (20061109/ED)
HIGHEST GRANTED PATENT NUMBER: US7134145
HIGHEST APPLICATION PUBLICATION NUMBER: US2006253949
CA INDEXING IS CURRENT THROUGH 7 Nov 2006 (20061107/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 9 Nov 2006 (20061109/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006


=> D QUE L65 NOS
L61             STR
L62 (          3)SEA FILE=REGISTRY FAM FUL L61
L63 (         14)SEA FILE=USPATFULL ABB=ON  PLU=ON  L62
L64 (          7)SEA FILE=USPATFULL ABB=ON  PLU=ON  LIDADRONIC ACID OR IG 9402
L65           14 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L63 OR L64)


=> S L65 NOT L38
L71          12 L65 NOT L38

=> DUP REM L69 L66 L67 L71 L68 L70
DUPLICATE IS NOT AVAILABLE IN 'PHAR'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
FILE 'MEDLINE' ENTERED AT 12:03:22 ON 09 NOV 2006

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PROCESSING COMPLETED FOR L69
PROCESSING COMPLETED FOR L66
PROCESSING COMPLETED FOR L67
PROCESSING COMPLETED FOR L71
PROCESSING COMPLETED FOR L68
PROCESSING COMPLETED FOR L70
L72           30 DUP REM L69 L66 L67 L71 L68 L70 (2 DUPLICATES REMOVED)
                 ANSWER '1' FROM FILE MEDLINE
                 ANSWER '2' FROM FILE BIOSIS
                 ANSWERS '3-5' FROM FILE DRUGU
                 ANSWERS '6-17' FROM FILE USPATFULL
                 ANSWERS '18-29' FROM FILE HCAPLUS
                 ANSWER '30' FROM FILE PHAR

=> D IALL 1; D IALL 2; D IALL 3-5; D IBIB ABS HITSTR 6-17; D IBIB ED ABS HITSTR 18-
29; D IALL 30

L72  ANSWER 1 OF 30     MEDLINE on STN                    DUPLICATE 1
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ACCESSION NUMBER: 2003122966 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12469251
TITLE: Modulation of cytosolic calcium levels in osteoblast-like osteosarcoma cells by olpadronate and its amino-derivative **IG-9402**.
AUTHOR: Vazquez G; Santillan G; Boland R; Roldan E; Perez-Lloret A
CORPORATE SOURCE: Departamento de Biologia, Bioquimica y Farmacia, Universidad Nacional del Sur, San Juan 670, (8000) Bahia Blanca, Argentina.
SOURCE: Calcified tissue international, (2003 Mar) Vol. 72, No. 3, pp. 215-21. Electronic Publication: 2002-12-10. Journal code: 7905481. ISSN: 0171-967X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 16 Mar 2003
Last Updated on STN: 4 Nov 2003
Entered Medline: 3 Nov 2003

ABSTRACT:
The molecular mechanisms as well as the structure/activity relationships involved in the antiresorptive actions of bisphosphonates on bone cells are still not clear. Replacement of the R1-hydroxyl by an NH2 group in olpadronate (OPD) abolishes its antiresorptive activity. We show here that in the rat osteosarcoma-derived osteoblast-like ROS 17/2.8 cell line, OPD and **IG-9402** (NH2-OPD; [3-(N,N-dimethylamine)-1-aminopropylidene bisphosphonate]), similar to 1,25(OH)2-vitamin D3, rapidly modulate cytosolic calcium levels ([Ca2+]i). As for the steroid hormone, the osteosarcoma cell Ca2+i response to OPD was rapid (30 sec) and sustained (>5 min), exhibiting a biphasic profile. The response to **IG-9402** was also fast but smaller than that of OPD and 1,25(OH)2D3, and rapidly declined to levels near basal. The effect of these bisphosphonates on [Ca2+]i was dose-dependent, being maximal at 10(-8) M and was not observed in non-bone cellular systems, e.g., skeletal muscle and breast cells. Pretreatment of the ROS 17/2.8 cells with the Ca2+ channel blockers nifedipine and verapamil markedly reduced (>70%) the influx phase of the response to OPD and almost completely inhibited that of ***IG*** **-9402**, indicating the participation of voltage-dependent Ca2+ channels in the action of both compounds. Moreover, preincubation with the phospholipase C inhibitors U73122 and neomycin or depletion of inner stores with thapsigargin completely blocked the response to either olpadronate or its amino-derivative. Both OPD and **IG-9402** significantly increased osteocalcin release into the culture medium of osteosarcoma cells. The results support the involvement of the Ca2+ signaling pathway as part of the mechanism by which bisphosphonates induce bone cellular responses.

CONTROLLED TERM:
Animals
Calcitriol: PD, pharmacology
Calcium Channel Blockers: PD, pharmacology
Calcium Channels: DE, drug effects
Calcium Channels: PH, physiology
*Calcium Signaling: DE, drug effects
Chick Embryo
*Cytosol: DE, drug effects
Cytosol: ME, metabolism
*Diphosphonates: PD, pharmacology
Dose-Response Relationship, Drug
Estrenes: PD, pharmacology
Neomycin: PD, pharmacology
Nifedipine: PD, pharmacology
*Osteoblasts: DE, drug effects

Osteoblasts: ME, metabolism
Osteocalcin: ME, metabolism
Osteosarcoma: ME, metabolism
Phospholipase C: AI, antagonists & inhibitors
Pyrrolidinones: PD, pharmacology
Rats
Research Support, Non-U.S. Gov't
Thapsigargin: PD, pharmacology
Tumor Cells, Cultured
Verapamil: PD, pharmacology

CAS REGISTRY NO.: 104982-03-8 (Osteocalcin); 112648-68-7 (1-(6-((3-methoxyestra-1,3,5(10)-trien-17-yl)amino)hexyl)-1H-pyrrole-2,5-dione); 1404-04-2 (Neomycin); 21829-25-4 (Nifedipine); 32222-06-3 (Calcitriol); 52-53-9 (Verapamil); 63132-39-8 (olpadronic acid); 67526-95-8 (Thapsigargin)

CHEMICAL NAME: 0 (Calcium Channel Blockers); 0 (Calcium Channels); 0 (Diphosphonates); 0 (Estrenes); 0 (Pyrrolidinones); EC 3.1.4.3 (Phospholipase C)

L72 ANSWER 2 OF 30 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:432676 BIOSIS Full-text

DOCUMENT NUMBER: PREV199900432676

TITLE: Differential effects of olpadronate and its aminosubstituted analog **IG-9402** on the regulation of cytosolic calcium in cultured rat osteoblasts.

AUTHOR(S): Vazquez, G. [Reprint author]; Boland, R. [Reprint author]; Roldan, E.; Perez-Lloret, A.

CORPORATE SOURCE: Dept. Biologia, Bioquimica and Farmacia, Universidad Nacional del Sur, Bahia Blanca, Argentina

SOURCE: Journal of Bone and Mineral Research, (Sept., 1999) Vol. 14, No. SUPPL. 1, pp. S239. print.
Meeting Info.: Twenty-First Annual Meeting of the American Society for Bone and Mineral Research. St. Louis, Missouri, USA. September 30-October 4, 1999. American Society for Bone and Mineral Research.
CODEN: JBMREJ. ISSN: 0884-0431.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 18 Oct 1999
Last Updated on STN: 3 May 2000

CONCEPT CODE: Pharmacology - General 22002
Cytology - Animal 02506
Pathology - Therapy 12512
Metabolism - General metabolism and metabolic pathways 13002
Bones, joints, fasciae, connective and adipose tissue - General and methods 18001
General biology - Symposia, transactions and proceedings 00520

INDEX TERMS: Major Concepts
Cell Biology; Metabolism; Pharmacology; Skeletal System (Movement and Support)

INDEX TERMS: Parts, Structures, & Systems of Organisms
osteoblast: skeletal system, cultured cells

INDEX TERMS: Chemicals & Biochemicals

cytosolic calcium; olpadronate: antiresorptive potency, bone fragility effects, calcium ion homeostasis effects; IG-9402: aminosubstituted olpadronate analog, calcium ion homeostasis effects, bone fragility effects, antiresorptive potency

INDEX TERMS: Miscellaneous Descriptors
Meeting Abstract

ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rat
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: 121368-58-9 (olpadronate)
63132-38-7 (IG-9402)

L72 ANSWER 3 OF 30 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN DUPLICATE 2
ACCESSION NUMBER: 2000-04189 DRUGU P E Full-text
TITLE: Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin.
AUTHOR: Plotkin L I; Weinstein R S; Parfitt A M; Roberson P K; Manolagas S C; Bellido T
CORPORATE SOURCE: Univ.Arkansas
LOCATION: Little Rock, Ark., USA
SOURCE: J.Clin.Invest. (104, No. 10, 1363-74, 1999) 12 Fig. 2 Tab. 68 Ref.
CODEN: JCINAO ISSN: 0021-9738
AVAIL. OF DOC.: Division of Endocrinology, University of Arkansas for Medical Sciences, 4301 West Markham, Mail Slot 587, Little Rock, Arkansas 72205, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

The effect was studied of etidronate (ET), alendronate (AD), pamidronate (PM), olpadronate (OP) and IG-9402 (amino-olpadronate, all Gador) on osteocyte and osteoblast apoptosis using murine osteocytic MLO-Y4 and murine osteoblastic cells. These bisphosphonates (BP) inhibited apoptosis. A similar effect was seen with calcitonin-salmon (CT, Bachem). The antiapoptotic effect of the BP and CT was associated with a rapid increase in the phosphorylated fraction of extracellular signal regulated kinases (ERK). AD, given s.c., abolished the increased apoptosis in vertebral cancellous bone osteocytes and osteoblasts in mice. The results suggest that the therapeutic efficacy of BP or CT may be partly due to their ability to prevent osteocyte and osteoblast apoptosis.

SECTION HEADING: P Pharmacology
E Endocrinology

CLASSIF. CODE: 24 Bones and Joints
49 Peptide Hormones
72 New Drugs

73 Trial Preparations

CONTROLLED TERM:
DRUG-COMPARISON *FT; MOUSE *FT; IN-VITRO *FT; MLOY4-CELL *FT; APOPTOSIS *FT; OSTEOCLAST *FT; OSTEOBLAST *FT; MODE-OF-ACT. *FT; LAB.ANIMAL *FT; BONE *FT
[01] ETIDRONATE *PH; GADOR *FT; ETIDRONAT *RN; CHELATORS *FT; PH *FT
CAS REGISTRY NO.: 2809-21-4
[02] ALENDRONATE *PH; GADOR *FT; OSTEOPOROSIS *OC; OSTEOPATHY *OC; PREDNISOLONE *RC; MK-217 *RN; MOUSE *FT; IN-VIVO *FT; S.C. *FT; LAB.ANIMAL *FT; INJECTION *FT; CHELATORS *FT; PH *FT
CAS REGISTRY NO.: 66376-36-1
[03] PAMIDRONATE *PH; GADOR *FT; APD *RN; CHELATORS *FT; PH *FT
CAS REGISTRY NO.: 40391-99-9
[04] OLPADRONATE *PH; OLPADRONA *RN; GADOR *FT; CHELATORS *FT; PH *FT
CAS REGISTRY NO.: 63132-39-8
[05] **IG-9402** *PH; DR0013206 *RN; GADOR *FT; CHELATORS *FT; TRIAL-PREP. *FT; NEW *FT; PH *FT
[06] CALCITONIN-SALMON *PH; BACHEM *FT; CALCITOSA *RN; THYROID-HORMONE *FT; THYROID-HORMONES *FT; PH *FT
CAS REGISTRY NO.: 47931-85-1
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L72 ANSWER 4 OF 30 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 71358 DRUGU
FILE SEGMENT: Registry
DERWENT DRUG REGISTRY NAME: DR0013206
DERWENT DRUG NAME: **IG-9402**
CONTROLLED TERM: CHELATORS; TRIAL-PREP.

L72 ANSWER 5 OF 30 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 66407 DRUGU
FILE SEGMENT: Registry
DERWENT DRUG REGISTRY NAME: DR0001135
DERWENT DRUG NAME: **LIDADRONIC ACID**
CAS REGISTRY NUMBER: **63132-38-7**
SUBSTRUCTURE TERM: PHOSPHONIC-ACID; POLYAMINE

L72 ANSWER 6 OF 30 USPATFULL on STN
ACCESSION NUMBER: 2005:209535 USPATFULL Full-text
TITLE: Phosphonate compounds
INVENTOR(S): Hostetler, Karl Y., Del Mar, CA, UNITED STATES
Beadle, James R., San Diego, CA, UNITED STATES
Kini, Ganesh D., Bristow, VA, UNITED STATES
PATENT ASSIGNEE(S): THE REGENTS OF THE UNIVERSITY OF CALIFORNIA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005182019	A1	20050818
	US 7098197	B2	20060829
APPLICATION INFO.:	US 2005-101259	A1	20050406 (11)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2004-759345, filed on 15 Jan 2004, PENDING Continuation of Ser. No. US

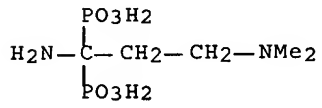
2002-148374, filed on 6 Nov 2002, GRANTED, Pat. No. US 6716825 A 371 of International Ser. No. WO 2000-US33079, filed on 4 Dec 2000

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-168813P	19991203 (60)
	US 2000-205719P	20000519 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Lisa A. Haile, J.D., Ph.D., DLA PIPE RUDNICK GRAY CARY US LLP, Suite 1100, 4365 Executive Drive, San Diego, CA, 92121-2133, US
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1-15
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1295
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to phosphonate compounds, compositions containing them, processes for obtaining them, and their use for treating a variety of medical disorders, e.g., osteoporosis and other disorders of bone metabolism, cancer, viral infections, and the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **63132-38-7D**, derivs.
(phosphonate compds., and preparation thereof, for treating medical disorders)
RN 63132-38-7 USPATFULL
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



L72 ANSWER 7 OF 30 USPATFULL on STN
ACCESSION NUMBER: 2005:203248 USPATFULL Full-text
TITLE: Phosphonate compounds
INVENTOR(S): Hostetler, Karl Y., Del Mar, CA, UNITED STATES
Beadle, James R., San Diego, CA, UNITED STATES
Kini, Ganesh D., Bristow, VA, UNITED STATES
PATENT ASSIGNEE(S): THE REGENTS OF THE UNIVERSITY OF CALIFORNIA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005176673	A1	20050811
	US 7094772	B2	20060822
APPLICATION INFO.:	US 2005-100882	A1	20050406 (11)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2004-759345, filed on 15 Jan 2004, PENDING Continuation of Ser. No. US 2002-148374, filed on 6 Nov 2002, GRANTED, Pat. No. US 6716825 A 371 of International Ser. No. WO

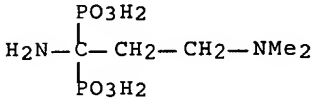
2000-US33079, filed on 4 Dec 2000

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-205719P	20000519 (60)
	US 1999-168813P	19991203 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Lisa A. Haile, J.D., Ph.D., DLA PIPER RUDNICK GRAY CARY US LLP, 4365 Executive Drive, Suite 1100, San Diego, CA, 92121-2133, US
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-15
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1284
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to phosphonate compounds, compositions containing them, processes for obtaining them, and their use for treating a variety of medical disorders, e.g., osteoporosis and other disorders of bone metabolism, cancer, viral infections, and the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **63132-38-7D**, derivs.
(phosphonate compds., and preparation thereof, for treating medical disorders)
RN 63132-38-7 USPATFULL
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



L72 ANSWER 8 OF 30 USPATFULL on STN
ACCESSION NUMBER: 2005:31433 USPATFULL Full-text
TITLE: Use of bisphosphonates for the treatment of osteogenesis imperfecta
INVENTOR(S): Roldan, Emilio J.A., Buenos Aires, ARGENTINA
Perez Lloret, Anibal, Buenos Aires, ARGENTINA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005026870	A1	20050203
APPLICATION INFO.:	US 2004-931858	A1	20040901 (10)

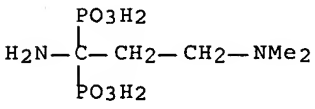
RELATED APPLN. INFO.: Division of Ser. No. US 2000-570275, filed on 12 May 2000, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	AR 1999-990102331	19990512

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PENDORF & CUTLIFF, 5111 MEMORIAL HIGHWAY, TAMPA, FL,

33634-7356
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: CLM-01-31
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 807
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This procedure consists in the first stage, of the administration of enough quantity of bisphosphonate preparation during the necessary period of time to acquire a degree of volumetric mineral density of the cortical tissue of application, within the normal range (average±1 DS). Then the administration of the bisphosphonate preparation is interrupted in order to enable the development of the sectional momentum of inertia. The length of the second stage can be determined by means of a tomography. That is to say, that the periods of administration or non-administration of the mineralizing agent are defined or controlled by precise osteologic variables and therefore are not fixed. If during the second stage the cortical mineral density drops by 6-10% of the maximum value previously obtained, administration of bishphosphonate preparation should be resumed until the corresponding maximum adjusted value is reached again. The proposed procedure of a period with bisphosphonate followed by another period without the bisphosphonate agent improves fracture resistance, provided that the length of both periods is controlled by defined osteologic variables.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **63132-38-7**, IG 9402
(IG 9402; bisphosphates for treatment of osteogenesis imperfecta)
RN 63132-38-7 USPATFULL
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



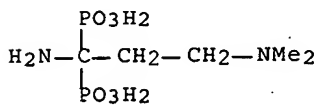
L72 ANSWER 9 OF 30 USPATFULL on STN
ACCESSION NUMBER: 2005:59177 USPATFULL Full-text
TITLE: Use of bisphosphonates for the treatment of osteogenesis imperfecta
INVENTOR(S): Roldan, Emilio J. A., Buenos Aires, ARGENTINA
Perez Lloret, Anibal, Buenos Aires, ARGENTINA
PATENT ASSIGNEE(S): Gador, S.A., ARGENTINA (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6864228	B1	20050308	
APPLICATION INFO.:	US 2000-570275		20000512	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Tate, Christopher
ASSISTANT EXAMINER: Teller, Roy
LEGAL REPRESENTATIVE: Pendorf & Cutliff
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 8 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT: 839
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This procedure consists in the first stage, of the administration of enough quantity of bisphosphonate preparation during the necessary period of time to acquire a degree of volumetric mineral density of the cortical tissue of application, within the normal range (average IDS). Then the administration of the bisphosphonate preparation is interruption in order to enable the development of the sectional momentum of inertia. The length of the second stage can be determined by means of a tomography. That is to say, that the periods of administration or non-administration of the mineralizing agent are defined or controlled by precise osteologic variables and therefore are not fixed. If during the second stage the cortical mineral density drops by 6-10% of the maximum value previously obtained, administration of bisphosphonate preparation should be resumed until the corresponding maximum adjusted value is reached again. The proposed procedure of a period with bisphosphonate followed by another period without the bisphosphonate agent improves fracture resistance, provided that the length of both periods is controlled by defined osteologic variables.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **63132-38-7**, IG 9402
(bisphosphonates sequential administration for treatment of osteogenesis imperfecta)
RN 63132-38-7 USPATFULL
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



L72 ANSWER 10 OF 30 USPATFULL on STN
ACCESSION NUMBER: 2004:166245 USPATFULL Full-text
TITLE: Phosphonate compounds
INVENTOR(S): Hostetler, Karl Y., Del Mar, CA, UNITED STATES
Beadle, James R., San Diego, CA, UNITED STATES
Kini, Ganesh D., Bristow, VA, UNITED STATES
PATENT ASSIGNEE(S): THE REGENTS OF THE UNIVERSITY OF CALIFORNIA (U.S. corporation)

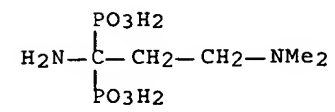
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004127735	A1	20040701
	US 7034014	B2	20060425
APPLICATION INFO.:	US 2004-759345	A1	20040115 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-148374, filed on 6 Nov 2002, GRANTED, Pat. No. US 6716825 A 371 of International Ser. No. WO 2000-US33079, filed on 4 Dec 2000, PENDING

NUMBER	DATE

PRIORITY INFORMATION: US 1999-168813P 19991203 (60)
US 2000-205719P 20000519 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Lisa A. Haile, J.D., Ph.D., GRAY CARY WARE & FREIDENRICH LLP, Suite 1100, 4365 Executive Drive, San Diego, CA, 92121-2133
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1331
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to phosphonate compounds, compositions containing them, processes for obtaining them, and their use for treating a variety of medical disorders, e.g., osteoporosis and other disorders of bone metabolism, cancer, viral infections, and the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **63132-38-7D**, derivs.
(phosphonate compds., and preparation thereof, for treating medical disorders)
RN 63132-38-7 USPATFULL
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



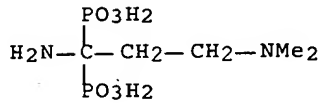
L72 ANSWER 11 OF 30 USPATFULL on STN
ACCESSION NUMBER: 2004:114704 USPATFULL Full-text
TITLE: Composition comprising bisphosphonates for prevention and/or treatment of metabolic diseases of bones, process for preparing such composition and use thereof
INVENTOR(S): Zanetti, Daniel, Buenos Aires, ARGENTINA
Cairatti, Damian, Buenos Aires, ARGENTINA
Piccinni, Enrique, Buenos Aires, ARGENTINA
Roldan, Emilio J.A., Buenos Aires, ARGENTINA
Papapoulos, Socrates, Leiden, NETHERLANDS

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004087550	A1	20040506	
APPLICATION INFO.:	US 2003-466897	A1	20031212	(10)
	WO 2001-EP690		20010123	

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Stephan A Pendorf, Pendorf & Cutliff, 5111 Memorial Highway, Tampa, FL, 33634-7356
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 427
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a composition for prevention and/or treatment of metabolic diseases of bones comprising at least one bisphosphonate; viscosity agents comprising carboxymethylcellulose and xanthan gum; at least one flavouring agent; and purified water; a process for preparing a composition according to the present invention; and use of such a composition for prevention, treatment and/or diagnosis of metabolic diseases of bones, especially for children.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **63132-38-7**
(composition comprising bisphosphonates for prevention and/or treatment of metabolic diseases of bones)
RN 63132-38-7 USPATFULL
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



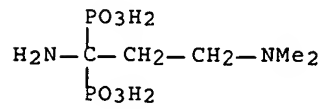
L72 ANSWER 12 OF 30 USPATFULL on STN
ACCESSION NUMBER: 2004:25390 USPATFULL Full-text
TITLE: PHOSPHONATE COMPOUNDS
INVENTOR(S): Hostetler, Karl Y., Del Mar, CA, UNITED STATES
Beadle, James R., San Diego, CA, UNITED STATES
Kini, Ganesh D., Bristow, VA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004019232	A1	20040129	
	US 6716825	B2	20040406	
APPLICATION INFO.:	US 2002-148374	A1	20021106	(10)
	WO 2000-US33079		20001204	

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Lisa A Haile J D, Gray Cary Ware & Freidenrich, Suite 1100, 4365 Executive Drive, San Diego, CA, 92121-2133
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1328
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to phosphonate compounds, compositions containing them, processes for obtaining them, and their use for treating a variety of medical disorders, e.g., osteoporosis and other disorders of bone metabolism, cancer, viral infections, and the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **63132-38-7D**, derivs.
(phosphonate compds., and preparation thereof, for treating medical disorders)
RN 63132-38-7 USPATFULL

CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



L72 ANSWER 13 OF 30 USPATFULL on STN

ACCESSION NUMBER:	2003:3107 USPATFULL Full-text		
TITLE:	Compounds and methods for modulating cerebral amyloid angiopathy		
INVENTOR(S):	Green, Allan M., Cambridge, MA, UNITED STATES Gervais, Francine, Ile Bizard, CANADA		

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003003141	A1	20030102
	US 6670399	B2	20031230
APPLICATION INFO.:	US 2000-747408	A1	20001222 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-171877P	19991223 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109
NUMBER OF CLAIMS:	77
EXEMPLARY CLAIM:	1
LINE COUNT:	1933

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides methods of inhibiting cerebral amyloid angiopathy. The invention further provides methods of treating a disease state characterized by cerebral amyloid angiopathy in a subject.

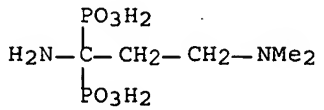
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

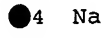
IT **373645-02-4**

(inhibitors of amyloid β peptide for modulating cerebral amyloid angiopathy)

RN 373645-02-4 USPATFULL

CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis-, tetrasodium salt (9CI) (CA INDEX NAME)





L72 ANSWER 14 OF 30 USPATFULL on STN
ACCESSION NUMBER: 2002:167863 USPATFULL Full-text
TITLE: Increasing bone strength with selected bisphosphonates
INVENTOR(S): Manolagas, Stavros C., Little Rock, AR, United States
Bellido, Teresita, Little Rock, AR, United States
PATENT ASSIGNEE(S): Board of Trustees of the University of Arkansas, Little Rock, AK, United States (U.S. corporation)

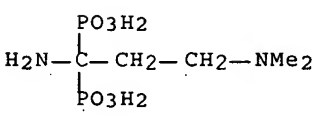
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6416737	B1	20020709
APPLICATION INFO.:	US 1999-443841		19991119 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-109237P	19981119 (60)
	US 1999-165480P	19991115 (60)

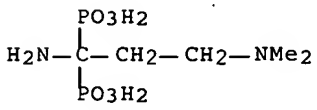
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Dees, Jose G.
ASSISTANT EXAMINER: Choi, Frank
LEGAL REPRESENTATIVE: King & Spalding, Knowles, Sherry M., Bennett-Paris, Joseph M.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 2491
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is a method and composition to increase bone strength in a manner that decreases fracture incidence, which may or may not include increasing bone mineral density ("BMD"). The invention includes administering an effective amount of a bisphosphonate to a host in need thereof to increase bone strength, which inhibits the apoptosis of osteoblasts and osteocytes, without a significant effect on osteoclasts. In one embodiment, the bisphosphonate is not 1-amino-3-(N,N-dimethylamino)-propyliden-1,1-bisphosphonic acid or its pharmaceutically acceptable salt. An increase in osteoblast life span can lead to an increase in bone mass, i.e., an anabolic effect. Preservation of osteocyte life span can increase bone strength, which may be disproportional to the increase in bone mass.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **63132-38-7**, IG 9402 **63132-38-7D**, IG 9402, salts
(increasing bone strength with selected bisphosphonates)
RN 63132-38-7 USPATFULL
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



RN 63132-38-7 USPATFULL
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



L72 ANSWER 15 OF 30 USPATFULL on STN

ACCESSION NUMBER:	1999:151201 USPATFULL Full-text
TITLE:	Therapeutic use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid and its salts
INVENTOR(S):	Van Beek, Ermond R., Leiden, Netherlands Lowik, Clemens W. G. M., Leiden, Netherlands Papapoulos, Socrates, Leiden, Netherlands Labriola, Rafael, Pilar, Argentina Vecchioli, Adriana, Pilar, Argentina
PATENT ASSIGNEE(S):	Gador, S.A., Argentina (non-U.S. corporation) University of Leiden, Netherlands (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5990098		19991123	
	WO 9702827		19970130	
APPLICATION INFO.:	US 1998-983247		19980901	(8)
	WO 1996-EP2981		19960708	
			19980901	PCT 371 date
			19980901	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	EP 1995-110706	19950710

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Geist, Gary
ASSISTANT EXAMINER:	Oh, Taylor Victor
LEGAL REPRESENTATIVE:	Pendorf & Cutliff
NUMBER OF CLAIMS:	18
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT:	363

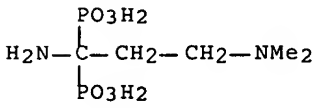
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Use of 1-amino-3-N,N-dimethylamino)-propyliden-1,1-bisphosphonic acid of the structural formula: ##STR1## or of its monosodium or other pharmaceutically acceptable salt, as a biological carrier for bone active substances or for the preparation of a medicament for the diagnosis, prophylaxis and/or treatment of bone and/or mineral metabolism disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **63132-38-7P**
(preparation and bone binding activity of amino-substituted bisphosphonic acids)

RN 63132-38-7 USPATFULL
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)

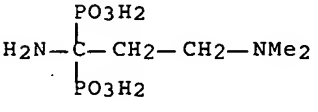


L72 ANSWER 16 OF 30 USPATFULL on STN
ACCESSION NUMBER: 85:68023 USPATFULL Full-text
TITLE: Treatment of collagenous tissue with glutaraldehyde and aminodiphosphonate calcification inhibitor
INVENTOR(S): Dewanjee, Mrinal K., Rochester, NM, United States
PATENT ASSIGNEE(S): Mayo Foundation, Rochester, MN, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4553974		19851119
APPLICATION INFO.:	US 1984-640725		19840814 (6)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Clingman, A. Lionel
LEGAL REPRESENTATIVE: Knuth, Charles J., Richardson, Peter C., Dryer, Mark
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 768
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A process for the treatment of collagenous tissue to adapt it for use in a prosthetic implant and to promote the growth of endothelial cells thereon after implantation comprising treatment with at least one surfactant prior to fixation, treatment with agents which inhibit calcification and agents which resist attack by phagocytic cells and optional treatment with stabilizing agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **63132-38-7**
(collagenous tissue treatment with, for transplants)
RN 63132-38-7 USPATFULL
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



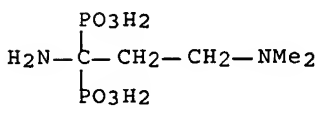
L72 ANSWER 17 OF 30 USPATFULL on STN
ACCESSION NUMBER: 77:56301 USPATFULL Full-text
TITLE: 1-Hydroxy-3-amino-alkane-1,1-diphosphonic acids and salts
INVENTOR(S): Blum, Helmut, Dusseldorf, Germany, Federal Republic of
Worms, Karl-Heinz, Dusseldorf, Germany, Federal Republic of
PATENT ASSIGNEE(S): Henkel & Cie GmbH, Dusseldorf-Holthausen, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4054598		19771018
APPLICATION INFO.:	US 1976-705792		19760716 (5)

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1975-2534391	19750801

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Evans, Joseph E.
LEGAL REPRESENTATIVE: Hammond & Littell
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
LINE COUNT: 424
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB 1-Hydroxy-3-amino-alkane-1,1-diphosphonic acids having the formula ##STR1## wherein X is a member selected from the group consisting of ##STR2## and ##STR3## wherein R.sub.1 is a member selected from the group consisting of hydrogen and alkyl having 1 to 3 carbon atoms and R.sub.2 is alkyl having 1 to 3 carbon atoms; as well as their water-soluble salts. The 1-hydroxy-3-amino-alkane-1,1-diphosphonic acids are excellent sequestering agents especially for alkaline earth metal ions. The compounds are useful in pharmaceutical preparations for treatment of disturbances of calcium or phosphate metabolism or cosmetic preparations such as toothpastes or mouthwashes for the prevention of tartar and plaque depositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **63132-38-7**
(diazotization and hydrolysis of)
RN 63132-38-7 USPATFULL
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



L72 ANSWER 18 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:986477 HCAPLUS Full-text
DOCUMENT NUMBER: 140:156750
TITLE: Quantitative Structure-Activity Relationships for γδ T Cell Activation by Bisphosphonates
AUTHOR(S): Sanders, John M.; Ghosh, Subhash; Chan, Julian M. W.; Meints, Gary; Wang, Hong; Raker, Amy M.; Song, Yongcheng; Colantino, Alison; Burzynska, Agnieszka; Kafarski, Pawel; Morita, Craig T.; Oldfield, Eric
CORPORATE SOURCE: Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL, 61801, USA
SOURCE: Journal of Medicinal Chemistry (2004), 47(2), 375-384
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:156750
ED Entered STN: 19 Dec 2003

AB γδ T cells are the first line of defense against many infectious organisms and are also involved in tumor cell surveillance and killing. They are stimulated by a broad range of small, phosphorus-containing antigens (phosphoantigens) as well as by the bisphosphonates commonly used in bone resorption therapy, such as pamidronate and risedronate. Here, we report the activation of γδ T cells by a broad range of bisphosphonates and develop a pharmacophore model for γδ T cell activation, in addition to using a comparative mol. similarity index anal. (CoMSIA) approach to make quant. relationships between γδ T cell activation by bisphosphonates and their three-dimensional structures. The CoMSIA analyses yielded R2 values of .apprx.0.8-0.9 and q2 values of .apprx.0.5-0.6 for a training set of 45 compds. Using an external test set, the activities (IC50 values) of 16 compds. were predicted within a factor of 4.5, on average The CoMSIA fields consisted of .apprx.40% hydrophobic, .apprx.40% electrostatic, and .apprx.20% steric interactions. Since bisphosphonates are known to be potent, nanomolar inhibitors of the mevalonate/isoprene pathway enzyme farnesyl pyrophosphate synthase (FPPS), we also compared the pharmacophores for γδ T cell activation with those for FPPS inhibition, using the Catalyst program. The pharmacophores for γδ T cell activation and FPPS inhibition both consisted of two neg. ionizable groups, a pos. charge feature and an endocyclic carbon feature, all having very similar spatial dispositions. In addition, the CoMSIA fields were quite similar to those found for FPPS inhibition by bisphosphonates. The activities of the bisphosphonates in γδ T cell activation were highly correlated with their activities in FPPS inhibition: R = 0.88, p = 0.002, vs. a human recombinant FPPS (N = 9 compds.); R = 0.82, p < 0.0001, for an expressed Leishmania major FPPS (N = 45 compds.). The bisphosphonate γδ T cell activation pharmacophore differs considerably, however, from that reported previously for γδ T cell activation by phosphoantigens (Gossman, W.; Oldfield, E. J. Med. Chemical 2002, 45, 4868-4874), suggesting different primary targets for the two classes of compds. The ability to quite accurately predict the activity of bisphosphonates as γδ T cell activators by using 3D QSAR techniques can be expected to help facilitate the design of addnl. bisphosphonates for potential use in immunotherapy.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

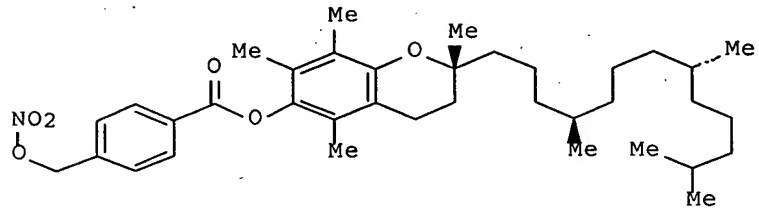
L72 ANSWER 19 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:652131 HCAPLUS Full-text
DOCUMENT NUMBER: 139:214237
TITLE: Preparation of nitrate prodrugs able to release nitric oxide in a controlled and selective way and their use

for prevention and treatment of inflammatory, ischemic and proliferative diseases

INVENTOR(S): Scaramuzzino, Giovanni
PATENT ASSIGNEE(S): Italy
SOURCE: Eur. Pat. Appl., 313 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1336602	A1	20030820	EP 2002-425075	20020213
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRIORITY APPLN. INFO.:			EP 2002-425075	20020213

ED Entered STN: 21 Aug 2003
GI



II

AB New pharmaceutical compds. of general formula F-(X)q (I) [q = 1-5, preferably 1; F is chosen among drugs such as δ-tocopherol, clidanac, diethylhomospermine, glucosamine, thymocartin, vofopitant, etc.; X is chosen among 4 groups M, T, V, and Y where M = ONO2, nitrate salt, nitrite ester, ONO, thoinitrite, SNO, etc., T = OR1-M, OR1OR1-M, SR1NR2R1-M, NR2R1-M, NR2R1SR1-M, etc., R1 = saturated or unsatd., linear or branched alkylene, having 1 to 21 carbon atoms or a saturated or unsatd., optionally heterosubstituted or branched cycloalkylene, having 3 to 7 carbon atoms or an optionally heterosubstituted arylene having 3 to 7 carbon atoms; R2 = H, saturated or unsatd., linear or branched 1-21 carbon atom alkyl, saturated or unsatd. optionally heterosubstituted or branched 3-7 carbon cycloalkyl, optionally heterosubstituted 3-7 carbon aryl; R1, R2 = OH, SH, F, Cl, Br, OPO3H2, CO2H, etc.; bond between F and T = carboxylic ester, carboxylic amide, glycoside, azo, thioester, sulfonic ester, etc.; V = Z-M2, OZ-M2, NR2Z-M2, R1Z-M2, OR1-M2, OR1Z-M2, M2 = M, R1-M, OR1-M, SR1-M, NR2R1-M; ZM2 = COCH2CH(M2)CH2N+Me3, COCH2CH2COM2, COCH(NHR2)CH2M2, etc.; Y = 4-COC6H4CH2ONO2, O(CH2)4ONO2, COCH(NH2)CH2ONO2, 3-OC6H4CH2ONO2, etc.] were prepared For example, α-tocopherol reacted with 4-HO2CC6H4CH2ONO2 to give the nitroxymethyl derivative II. The compds. of general formula I are nitrate prodrugs which can release nitric oxide in vivo in a controlled and selective way and without hypotensive side effects and for this reason they are useful for the preparation of medicines for prevention and treatment of inflammatory, ischemic, degenerative and proliferative diseases of musculoskeletal,

tegumental, respiratory, gastrointestinal, genito-urinary and central nervous systems.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 20 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:539062 HCAPLUS Full-text
DOCUMENT NUMBER: 137:226194
TITLE: Highly Potent Geminal Bisphosphonates. From Pamidronate Disodium (Aredia) to Zoledronic Acid (Zometa)
AUTHOR(S): Widler, Leo; Jaeggi, Knut A.; Glatt, Markus; Mueller, Klaus; Bachmann, Rolf; Bisping, Michael; Born, Anne-Ruth; Cortesi, Reto; Guiglia, Gabriela; Jeker, Heidi; Klein, Remy; Ramseier, Ueli; Schmid, Johann; Schreiber, Gerard; Seltenmeyer, Yves; Green, Jonathan R.
CORPORATE SOURCE: Arthritis and Bone Metabolism Therapeutic Area, Novartis Pharma Research, Basel, CH-4002, Switz.
SOURCE: Journal of Medicinal Chemistry (2002), 45(17), 3721-3738
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:226194
ED Entered STN: 19 Jul 2002
AB Bisphosphonates (BPs) are pyrophosphate analogs in which the oxygen in P-O-P has been replaced by a carbon, resulting in a metabolically stable P-C-P structure. Pamidronate (1b, Novartis), a second-generation BP, was the starting point for extensive SAR studies. Small changes of the structure of pamidronate lead to marked improvements of the inhibition of osteoclastic resorption potency. Alendronate (1c, MSD), with an extra methylene group in the N-alkyl chain, and olpadronate (1h, Gador), the N,N-di-Me analog, are about 10 times more potent than pamidronate. Extending one of the N-Me groups of olpadronate to a pentyl substituent leads to ibandronate (1k, Roche, Boehringer-Mannheim), which is the most potent close analog of pamidronate. Even slightly better antiresorptive potency is achieved with derivs. having a Ph group linked via a short aliphatic tether of three to four atoms to nitrogen, the second substituent being preferentially a Me group (e.g., 4g, 4j, 5d, or 5r). The most potent BPs are found in the series containing a heteroarom. moiety (with at least one nitrogen atom), which is linked via a single methylene group to the geminal bisphosphonate unit. Zoledronic acid (6i), the most potent derivative, has an ED50 of 0.07 mg/kg in the TPTX in vivo assay after s.c. administration. It not only shows by far the highest therapeutic ratio when comparing resorption inhibition with undesired inhibition of bone mineralization but also exhibits superior renal tolerability. Zoledronic acid (6i) has thus been selected for clin. development under the registered trade name Zometa. The results of the clin. trials indicate that low doses are both efficacious and safe for the treatment of tumor-induced hypercalcemia, Paget's disease of bone, osteolytic metastases, and postmenopausal osteoporosis.
REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 21 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:833023 HCAPLUS Full-text
DOCUMENT NUMBER: 135:376738
TITLE: Compounds and methods for modulating cerebral amyloid angiopathy using inhibitors of an amyloid β

peptide

INVENTOR(S): Green, Allan M.; Gervais, Francine

PATENT ASSIGNEE(S): Neurochem, Inc., Can.

SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001085093	A2	20011115	WO 2000-IB2078	20001222
WO 2001085093	A3	20020829		
WO 2001085093	C2	20020926		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2395314	AA	20011115	CA 2000-2395314	20001222
AU 2001084313	A5	20011120	AU 2001-84313	20001222
EP 1251837	A2	20021030	EP 2000-993855	20001222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2000016652	A	20021119	BR 2000-16652	20001222
US 2003003141	A1	20030102	US 2000-747408	20001222
US 6670399	B2	20031230		
JP 2003532656	T2	20031105	JP 2001-581748	20001222
AU 2006201445	A1	20060504	AU 2006-201445	20060406

PRIORITY APPLN. INFO.:	US 1999-171877P	P	19991223
	AU 2001-84313	A3	20001222
	WO 2000-IB2078	W	20001222

OTHER SOURCE(S): MARPAT 135:376738

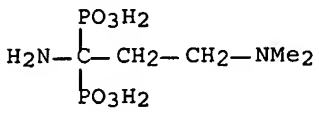
ED Entered STN: 16 Nov 2001

AB The invention provides methods of inhibiting cerebral amyloid angiopathy (CAA) and treating a disease state characterized by cerebral amyloid angiopathy, e.g., Alzheimer's disease, in a subject using an inhibitor of the 39-40 amino acid amyloid β peptide (Aβ40). The Aβ40 inhibitor is selected from, e.g., sulfonic acid derivs., such as ethanesulfonic acid, 1,2-ethanedisulfonic acid, 1-propanesulfonic acid, 1,3-propanedisulfonic acid, 1,4-butanedisulfonic acid, 1,5-pentanedisulfonic acid, 2-aminoethanesulfonic acid, 4-hydroxy-1-butanesulfonic acid, 1-butanesulfonic acid, 1-decanesulfonic acid, 2-propanesulfonic acid, 3-pentanesulfonic acid, 4-heptanesulfonic acid, etc., and pharmaceutically acceptable salts thereof or from from phosphonic acid derivs., such as diethylphosphonoacetic acid, phenylphosphonic acid, 3-aminopropylphosphonic acid, propylphosphonic acid, etc. The compds. are formulated in a dispersion system, a liposome formulation, or microspheres using a polymeric matrix. The polymeric matrix is selected from natural polymers, such as albumin, alginate, cellulose derivs., collagen, fibrin, gelatin, and polysaccharides, or synthetic polymers such as polyesters, polyethylene glycol, poloxamers, and polyanhydrides. For example, the ability of compds. of the invention to inhibit CAA was measured in 9 wk old hAPP transgenic mice treated with two different concns. of a compound of the present invention, 3-amino-1-propanesulfonic acid sodium salt, 100 and 30 mg/kg. Mice were administered the compound for 8 wk, after which they were

sacrificed and their brains were perfused and processed for histol. staining with Thioflavin S. This method may also be used as a screening method for determining activity of a candidate compound for inhibiting CAA. The extent of CAA in brain sections obtained from these animals was qual. determined following staining. The results indicate that the test compound was effective in (i) reducing the number of mice showing CAA, and (ii) showing an effect on the severity of the deposition seen in the brain vasculature of these animals.

IT **373645-02-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors of amyloid β peptide for modulating cerebral amyloid angiopathy)

RN 373645-02-4 HCAPLUS
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis-, tetrasodium salt (9CI) (CA INDEX NAME)



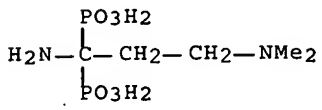
4 Na

L72 ANSWER 22 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:416728 HCAPLUS Full-text
DOCUMENT NUMBER: 135:14356
TITLE: Phosphonate compounds, and preparation thereof, for treating medical disorders
INVENTOR(S): Hostetler, Karl Y.; Beadle, James R.; Kini, Ganesh D.
PATENT ASSIGNEE(S): The Regents of the University of California, San Diego, USA
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001039724	A2	20010607	WO 2000-US33079	20001204
WO 2001039724	A3	20011018		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2393410	AA	20010607	CA 2000-2393410	20001204

AU 2001019497	A5	20010612	AU 2001-19497		20001204
EP 1233770	A2	20020828	EP 2000-982468		20001204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
BR 2000016058	A	20030715	BR 2000-16058		20001204
JP 2004500352	T2	20040108	JP 2001-541459		20001204
RU 2258707	C2	20050820	RU 2002-118327		20001204
US 2004019232	A1	20040129	US 2002-148374		20021106
US 6716825	B2	20040406			
ZA 2002004194	A	20030820	ZA 2002-4194		20021204
US 2004127735	A1	20040701	US 2004-759345		20040115
US 7034014	B2	20060425			
US 2005176673	A1	20050811	US 2005-100882		20050406
US 7094772	B2	20060822			
US 2005182019	A1	20050818	US 2005-101259		20050406
US 7098197	B2	20060829			
PRIORITY APPLN. INFO.:			US 1999-168813P	P	19991203
			US 2000-205719P	P	20000519
			WO 2000-US33079	W	20001204
			US 2002-148374	A1	20021106
			US 2004-759345	A1	20040115

OTHER SOURCE(S): MARPAT 135:14356
ED Entered STN: 08 Jun 2001
AB The invention discloses phosphonate compds., compns. containing them, processes for obtaining them, and their use for treating a variety of medical disorders, e.g. osteoporosis and other disorders of bone metabolism, cancer, and viral infections. Preparation of compds. of the invention, e.g. 1-O-hexadecylpropanediol-3-alendronate, is described.
IT **63132-38-7D**, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphonate compds., and preparation thereof, for treating medical disorders)
RN 63132-38-7 HCAPLUS
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



L72 ANSWER 23 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:351360 HCAPLUS Full-text
DOCUMENT NUMBER: 132:343333
TITLE: Increasing bone strength with selected bisphosphonates
INVENTOR(S): Manolagas, Stavros C.; Bellido, Teresita
PATENT ASSIGNEE(S): The Board of Trustees for the University of Arkansas, USA; Gador S.A.
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000028982	A2	20000525	WO 1999-US27528		19991119
WO 2000028982	A3	20020711			
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
AU 2000015257	A5	20000605	AU 2000-15257		19991119
US 6416737	B1	20020709	US 1999-443841		19991119
PRIORITY APPLN. INFO.:			US 1998-109237P	P	19981119
			US 1999-165480P	P	19991115
			WO 1999-US27528	W	19991119

ED Entered STN: 26 May 2000

AB The present invention is a method and composition to increase bone strength in a manner that decreases fracture incidence, which may or may not include increasing bone mineral d. ("BMD"). The invention includes administering an effective amount of a bisphosphonate to a host in need thereof to increase bone strength, which inhibits the apoptosis of osteoblasts and osteocytes, without a significant effect on osteoclasts. In one embodiment, the bisphosphonate is not 1-amino-3-(N,N-dimethylamino)- propyliden-1,1-bisphosphonic acid or its pharmaceutically acceptable salt. An increase in osteoblast life span can lead to an increase in bone mass, i.e., an anabolic effect. Preservation of osteocyte life span can increase bone strength, which may be disproportional to the increase in bone mass. Pretreatment of osteocytes with bisphosphonates for 1h before the addition of 10-6 M dexamethasone inhibited glucocorticoid-induced apoptosis, with minimal effective concentration between 10-9-10-8 M.

L72 ANSWER 24 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1986:430115 HCAPLUS Full-text
DOCUMENT NUMBER: 105:30115
TITLE: Treatment of collagenous tissue
INVENTOR(S): Dewanjee, Mrinal Kanti
PATENT ASSIGNEE(S): Mayo Foundation, USA
SOURCE: Eur. Pat. Appl., 32 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
EP 174737	A2	19860319	EP 1985-305681		19850809
EP 174737	A3	19870311			
R: BE, CH, DE, FR, GB, IT, LI, NL, SE					
DK 8503667	A	19860215	DK 1985-3667		19850813
AU 8546130	A1	19860327	AU 1985-46130		19850813
AU 558688	B2	19870205			
JP 61137825	A2	19860625	JP 1985-179218		19850814
PRIORITY APPLN. INFO.:			US 1984-640725	A	19840814

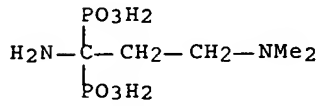
ED Entered STN: 26 Jul 1986

AB A process is given for the treatment of collagenous tissue to adapt it for use as a prosthetic implant and to promote the growth of endothelial cells thereon. The tissue is treated with at least 1 surfactant to remove deleterious material and open up the fibrous structure of the collagenous tissue, washed, fixed with glutaraldehyde, and the glutaraldehyde-fixed tissue is treated with a calcification-inhibiting agent, an agent that inhibits infiltration and attack by phagocytic cells and/or an agent that inhibits infection; and then the resulting matrix is treated with a reducing agent to stabilize the bonding of the agents and glutaraldehyde to the tissue. Thus, calf pericardial tissue was kept in Triton X100 for 3 h, washed, placed in 0.5% glutaraldehyde in 0.05M acetate buffer (pH 5.5) for 3.5 h, rinsed, and immersed in 3-amino-1-hydroxypropane-1,1- diphosphonic acid (16 mg/mL) in 0.05M acetate buffer, for 2-3 h. After 3 added cycles of immersion in glutaraldehyde (12 h)/rinsing, the tissue was soaked in 5 mg $NaBH_4$/mL for 30 min, rinsed, and stored in 0.5% glutaraldehyde. When valves made of this tissue were implanted in calves, there was no calcification, and abundant endothelial cell growth was observed

IT **63132-38-7**
RL: BIOL (Biological study)
(collagenous tissue treatment with, for transplants)

RN 63132-38-7 HCAPLUS

CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



L72 ANSWER 25 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1983:181876 HCAPLUS Full-text

DOCUMENT NUMBER: 98:181876

TITLE: Scale prevention with special reference to threshold treatment

AUTHOR(S): Van Rosmalen, G. M.

CORPORATE SOURCE: Dep. Chem., Delft Univ. Technol., Delft, 2628 RZ, Neth.

SOURCE: Chemical Engineering Communications (1983), 20(3-4), 209-33
CODEN: CEGCAK; ISSN: 0098-6445

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 12 May 1984

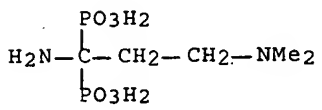
AB Various chemical, phys., and mech. methods for preventing deposition of mineral scale are described. The suitability of the different methods, which largely depends on the specific features and requirements of the system involved, is discussed. Special emphasis is placed upon the threshold treatment, where the growth process is retarded by the addition of trace amts. of growth inhibitors. Growth expts. were performed on $BaSO_4$ and $CaSO_4.2H_2O$ seed crystals, suspended in a supersatd. solution with and without organic bisphosphonates as inhibitors. Two methods are selected for the anal. of the growth data. A degree of inhibition is defined to obtain a quant. description of the growth-inhibitor effect on the growth rate. The effect of the mol.

structure of various bisphosphonates is shown. The effect of a bisphosphonate on the geometry of CaSO4.2H2O crystals is illustrated.

IT 63132-38-7
RL: USES (Uses)
(crystal growth rates of barium sulfate and calcium sulfate dihydrate in relation to)

RN 63132-38-7 HCAPLUS

CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



L72 ANSWER 26 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1983:597742 HCAPLUS Full-text

DOCUMENT NUMBER: 99:197742

TITLE: The influence of various phosphonates on the growth rate of barium sulfate crystals in suspension

AUTHOR(S): Van der Leeden, M. C.; Reedijk, J.; Van Rosmalen, G. M.

CORPORATE SOURCE: Dep. Chem., Delft Univ. Technol., Delft, 2628 RZ, Neth.

SOURCE: Estudios Geologicos (Madrid) (1982), 38(3-4), 279-87
CODEN: EGLMA9; ISSN: 0367-0449

DOCUMENT TYPE: Journal

LANGUAGE: English

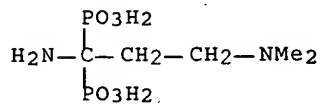
ED Entered STN: 12 May 1984

AB The growth of BaSO4 crystals on walls of petrochem. equipment can be slowed by phosphonates having dissociated PO32- groups and H-bonding groups, such as CO2H, OH, or/and NH3+ groups. HO2CCH2CH(CO2H)CH(PO3H2)2 [51395-42-7] and MeC(OH)(PO3H2)2 [2809-21-4] are especially effective.

IT 63132-38-7
RL: USES (Uses)
(barium sulfate scale inhibitors, for petrochem. equipment)

RN 63132-38-7 HCAPLUS

CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



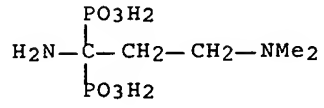
L72 ANSWER 27 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1980:181274 HCAPLUS Full-text

DOCUMENT NUMBER: 92:181274

TITLE: Synthesis of 2- and 3-substituted alkanediphosphonic

acids
AUTHOR(S): Worms, K. H.; Blum, H.; Hempel, H. U.
CORPORATE SOURCE: Henkel KGaA, Duesseldorf, D-4000/1, Fed. Rep. Ger.
SOURCE: Zeitschrift fuer Anorganische und Allgemeine Chemie (1979), 457, 214-18
CODEN: ZAACAB; ISSN: 0044-2313
DOCUMENT TYPE: Journal
LANGUAGE: German
ED Entered STN: 12 May 1984
AB Approx. 15 title compds. were prepared by phosphonylation of, primarily, aminoalkanoic acids and aminoalkanonitriles. Thus, 1 mol H3PO3, 1 mol PCl3, 330 mL PhCl and 0.5 mol Et2N(CH2)2CO2H gave 57% Et2N(CH2)2C(OH)[P(O)(OH)2]2. Similarly prepared were Me2C(NH2)C(OH)[P(O)(OH)2]2, MeCH(NH2)CH2C(OH)[P(O)(OH)2]2, H2NCH2CH2C(OH)[P(O)(OH)2]2, and H2NCHPhCH2C(OH)[P(O)(OH)2]2. Phosphonylation of 0.25 mol H2NCH2CH2CN in 100 mL dioxane with 0.5 mol PBr3 followed by hydrolysis gave H2NCH2CH2C(NH2)[P(O)(OH)2]2. Similarly prepared, were MeCH(NH2)CH2C(NH2)[P(O)(OH)2]2, MeNHCH2CH2C(NH2)[P(O)(OH)2]2, and Me2NCH2CH2C(NH2)[P(O)(OH)2]2.
IT **63132-38-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction with nitrous acid)
RN 63132-38-7 HCAPLUS
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI) (CA INDEX NAME)



L72 ANSWER 28 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1977:468491 HCAPLUS Full-text
DOCUMENT NUMBER: 87:68491
TITLE: 1-Hydroxy-3-aminoalkane-1,1-diphosphonic acids
INVENTOR(S): Blum, Helmut; Worms, Karl Heinz
PATENT ASSIGNEE(S): Henkel und Cie. G.m.b.H., Fed. Rep. Ger.
SOURCE: Ger. Offen., 13 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2534391	A1	19770217	DE 1975-2534391	19750801
DE 2534391	C2	19830113		
NL 7607703	A	19770203	NL 1976-7703	19760712
US 4054598	A	19771018	US 1976-705792	19760716
BE 844649	A1	19770131	BE 1976-169348	19760729
JP 52019628	A2	19770215	JP 1976-91196	19760730
JP 59025798	B4	19840621		
CH 599234	A	19780531	CH 1976-9788	19760730

GB 1540238	A	19790207	GB 1976-31891		19760730
AT 349642	B	19790410	AT 1976-5633		19760730
AT 350161	B	19790510	AT 1976-5631		19760730
AT 7605631	A	19781015			
CH 620359	A	19801128	CH 1976-9789		19760730
PRIORITY APPLN. INFO.:			DE 1975-2534391	A	19750801

ED Entered STN: 12 May 1984

AB RCH2C(OH)[P(O)(OH)2]2 (I, R = Me2NCH2, Et2NCH2, H2NCHMe) were prepared e.g. by treating RCH2CO2H with H3PO3 and P trihalide. I complex with 710 to 2500 mg CaCO3/g I at pH 11.

L72 ANSWER 29 OF 30 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1977:423490 HCAPLUS Full-text
DOCUMENT NUMBER: 87:23490
TITLE: 1,3-Diaminoalkane-1,1-diphosphonic acids
INVENTOR(S): Blum, Helmut; Worms, Karl Heinz
PATENT ASSIGNEE(S): Henkel und Cie. G.m.b.H., Fed. Rep. Ger.
SOURCE: Ger. Offen., 14 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
DE 2534390	A1	19770217	DE 1975-2534390		19750801
DE 2534390	C2	19830113			
NL 7607702	A	19770203	NL 1976-7702		19760712
NL 186575	B	19900801			
NL 186575	C	19910102			
BE 844648	A1	19770131	BE 1976-169347		19760729
JP 52019627	A2	19770215	JP 1976-91195		19760730
JP 59025797	B4	19840621			
FR 2319645	A1	19770225	FR 1976-23296		19760730
CH 599233	A	19780531	CH 1976-9786		19760730
AT 347591	B	19790110	AT 1976-5632		19760730
GB 1540239	A	19790207	GB 1976-31892		19760730
AT 350160	B	19790510	AT 1976-5630		19760730
AT 7605630	A	19781015			
CH 620358	A	19801128	CH 1976-9787		19760730
PRIORITY APPLN. INFO.:			DE 1975-2534390	A	19750801

ED Entered STN: 12 May 1984

AB RCH2C(NH2)[P(O)(OH)2]2 (I, R = Me2NCH2, MeNHCH2, H2NCH2, H2NCHMe) were prepared by treating RCH2CN with PBr3 and H2O. I complex 630->2500 mg CaCO3/g I at pH 11 and can be used for water softening and in the treatment of calcification disorders.

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L72 ANSWER 30 OF 30 PHAR COPYRIGHT 2006 Informa UK Ltd on STN
AN 14466 PHAR
DN 025567
CN lidadronate
CN **IG-9402**
CN Phosphonic acid, (1-amino-3-(dimethylamino)propylidene)bis- (CAS)
RN **63132-38-7**
MF C5 H16 N2 O6 P2
MW 262.14
HAC 8
HD 6
LOGP -.74
FRB 9
STA Ceased

CO

Type	Company Name (Country)	Development Status
Originator	Gador (Argentina)	No Development Reported

PI WO 9702827
PRAI GB 19950707
SO Pharmaprojects. PJB Publications Ltd., Richmond, Surrey, UK
TX Lidadronate (**IG-9402**) was under development by
Gador for the treatment of urolithiasis, osteoporosis, periodontal diseases and other bone disorders (Direct communication, Gador, 23 Jan 2001). It is orally-active, and inhibits glucocorticoid-induced osteocyte apoptosis (Direct communications, Gador, 25 Jan 1999 and 28 Jan 2002).

Preclinical

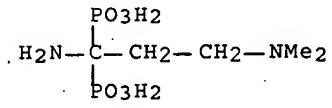
In vivo, it showed no interference with resorptive bone metabolism (Direct communication, Gador, 28 Jan 2002). Lidadronate and analogues are patented as selective modulators of osteoblast-osteocyte cells (Direct communication, Gador, 25 Jan 1999). Updated by JB on 19/2/2002.
DSTA World: No Development Reported
Argentina: Preclinical
CC G4Z Urological
A1A Stomatological
M5A Osteoporosis treatment
CT Indication: Unspecified (No Development Reported)
GEN Target Gene: Unspecified
ORGM CH-SY (Chemical, synthetic)
RTE A-PO (Alimentary, po)
RDAT 20031211 RNTE ##Actual; No Development Reported
20010123 ##Estimated; Names Granted **IG-9402**
19970415 ##Estimated; New Product in Pharmaprojects
PHCD OSTEOBL-AG; Osteoblast stimulant; Physiological, Biochemical, Osteoblast stimulant; P-B-OSTEOBL-AG.
PHCD OSTEOBL-AN; Osteoblast inhibitor; P=Biochemical, OSTEO; P=B-OSTEOCL-AN.
PHCD APOP-AN; Apoptosis antagonist; Physiological, Biochemical, Apoptosis antagonist; General apoptosis antagonist; Apoptosis inhibitor; P-B-APOP-AN.
PHCD P; P-B; P-B-OSTEOBL; P-B-OSTEOBL-AG; P-OSTEOBL; P-OSTEOBL-AG; P-AG; B; B-OSTEOBL; B-OSTEOBL-AG; B-AG; OSTEOBL; OSTEOBL-AG; P-B-AG; P=B; P=B-OSTEOCL; P=B-OSTEOCL-AN; P=B-AN; OSTEOCL; OSTEOCL-AN; P-B-APOP;

P-B-APOP-AN; P-APOP; P-APOP-AN; P-AN; B-APOP; B-APOP-AN; B-AN; APOP; APOP-AN; P-B-AN.

LN

Therapy (CC)	Pharmacology (PHCD)	Status (DSTC)
G4Z	OSTEOBL-AG OSTEOBL-AN APOP-AN	N
A1A	OSTEOBL-AG OSTEOBL-AN APOP-AN	N
M5A	OSTEOBL-AG OSTEOBL-AN APOP-AN	N

LCDAT 20031211: IL : No development reported



keyword:pediatric AND keyword:osteoporosis [Search]

☑ Journal sources ☑ Preferred Web sources ☑ Other Web sources ☐ Exact phrase

Searched for:: :All of the words:**keyword:pediatric** AND **keyword:osteoporosis**

Found:: :**7 total | 6 journal results | 0 preferred web results | 1 other web results**

Sort by:: :**relevance | date**

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humans
male
Or refine using:
All of the words
Refine

☐ **1.** Risk factors for low bone mineral density in children and young adults with Crohn's disease
Semeao, E.J. / Jawad, A.F. / Stouffer, N.O. / Zemel, B.S. / Piccoli, D.A. / Stallings, V.A., *The Journal of Pediatrics*, Nov 1999
Objective: Low bone mineral density (BMD) is a recognized complication of Crohn's disease (CD). The aim of this study was to identify the risk factors for low BMD in pediatric patients with CD. Study Design: One hundred nineteen subjects...
Published journal article available from ScienceDirect
similar results

☐ **2.** Interpretation of bone mineral density values in pediatric Crohn's disease.
Herzog, D / Bishop, N / Glorieux, F / Seidman, E G, *Inflammatory bowel diseases*, Nov 1998
Patients with Crohn's disease (CD) often have low bone mineral density (BMD) for their chronological age (CA). However, pediatric cases frequently have growth failure and delayed bone age (BA) and height age (HA). Do they really have the amount of ...
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☐ **3.** Pediatric scleroderma.
Emery, H, *Seminars in cutaneous medicine and surgery*, Mar 1998
Scleroderma is a diverse group of conditions which have in common fibrosis of skin and other tissues. Although less common in children than in adults, these conditions are an important cause of morbidity and occasional mortality when they occur in the ...
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☐ **4.** Methotrexate osteopathy, does it exist?
Maenaut, K / Westhovens, R / Dequeker, J, *The Journal of rheumatology*, Dec 1996
We describe 2 postmenopausal women with rheumatoid arthritis (RA). They developed fractures during their treatment with weekly low dose methotrexate (MTX). The adverse effect of longterm low dose regimens of MTX on bone metabolism has been described as ...

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☐ **5.** Complications of fractures elucidated by bone scans.
Williamson, S L / Seibert, J J / Glasier, C M / Williamson, M R, *Clinical nuclear medicine*, Apr 1987
Three pediatric cases are presented to demonstrate the value of bone scanning in this population to evaluate the fracture complications of nonunion and sequestrum formation.

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☐ **6.** [Systemic and biochemical manifestations of hepatoblastomas (author's transl)]
Mutz, I D / Urban, C E / Höllwarth, M, *Klinische Pädiatrie*, Jul 1978
Among 220 children with malignant solid tumors diagnosed at the University Children Hospital and Department of Pediatric Surgery in Graz six (1,8%) hepatoblastomas were found. All patients were boys. Systemic manifestations may precede the discovery of ...

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